APPENDIX A

UNITED STATES COURT OF APPEALS,
FEDERAL CIRCUIT

No. 2008-1282

BAYER SCHERING PHARMA AG and BAYER HEALTHCARE PHARMACEUTICALS, INC.,
Plaintiffs-Appellants,
v.
BARR LABORATORIES, INC.,
Defendant-Appellee.

Aug. 5, 2009.
Rehearing and Rehearing En Banc Denied Oct. 26, 2009.

Before NEWMAN, FRIEDMAN, and MAYER, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* MAYER. Dissenting opinion filed by *Circuit Judge* NEWMAN.

MAYER, *Circuit Judge*.

Bayer Schering Pharma AG ("Bayer") appeals the judgment of the United States District Court for the District of New Jersey, holding U.S. Patent No. 6,787,531 ("'531 Patent") invalid due to obviousness. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, No. 05-CV-2308, 2008 WL 628592 (D.N.J. March 3, 2008). Because we hold that the invention would have been obvious to try, we affirm.

BACKGROUND

Bayer is a large pharmaceutical company that produces the daily oral contraceptive, Yasmin®. One of the active ingredients in Yasmin, drospirenone, is a progestin that inhibits ovulation. Each of the invalidated claims requires drospirenone as the active ingredient. Drospirenone was known in the art at all times relevant. Its contraceptive qualities are particularly well suited for producing an oral contraceptive because, in addition to inhibiting ovulation, it is a diuretic which will diminish excess water retention arising from the estrogen component of oral contraceptives, and has anti-acne qualities to promote clear skin. These desirable qualities have led to Yasmin's success. Drospirenone is also acid-sensitive. When exposed to low-pH (highly acidic) environments such as found in the human stomach, drospirenone "isomerizes"—that is, the acid catalyzes a reaction that rearranges drospirenone's molecular structure while its molecular composition remains constant. The resulting isomer is non-antimineralocorticoidal, meaning it will not act as a diuretic, removing the desirable anti-bloating effect that sets drospirenone apart from other prior art progestins. Therefore, scientists working with drospirenone for use in an oral contraceptive must be aware of and work around the effects that the human stomach will have on the drug to ensure that its "bioavailability"—the amount of the active drug absorbed into the bloodstream and available to act on the body—is high enough to perform its contraceptive function.

Drospirenone is also a poorly water soluble hydrophobic composition. Because it will not easily dissolve into a volume of liquid, its bioavailability is degraded. To combat this, pharmaceutical producers commonly

employ a technique called "micronization," whereby the drug's particle size is reduced, increasing its overall surface area. Often (but not always) with a larger surface area, the dissolution rate is also increased, ensuring that all of the poorly water soluble drug that can dissolve will dissolve in a given volume of liquid. With more of the drug dissolved, the drug will exhibit a higher bioavailability. Indeed, Bayer's expert testified at trial that this would be his first choice in attempting to increase the dissolution rate because, among the different ways to increase the dissolution rate, micronization presents the best chance of success. All commercially available oral contraceptives use micronized progestins and/or estrogens, so this technique was well known in the art.

While micronizing a poorly water soluble composition may result in increased bioavailability, micronizing an acid-sensitive composition may also increase its sensitivity to the acid. A drug that isomerizes when exposed to acid thus may isomerize at a faster rate if it is micronized.

One method pharmaceutical companies use to surmount an acid-sensitivity problem with a drug to be taken orally is to deliver the drug via an enteric-coated pill, as opposed to an immediate release pill, also called a "normal pill." An enteric coating is a pH-sensitive film that protects the drug from stomach acid, and only releases the drug when it has passed into the less acidic duodenum and small intestine. However, enteric coatings are not without drawbacks themselves. Coated tablets including enteric coated tablets present an obstacle to absorption, and thus reduce the drug's exhibited bioavailability. Additionally, as was known in the art at the time, they introduce a significant delay in the onset of

therapeutic response while creating a considerable patient-to-patient variation of that onset. In fact, even for an individual taking the drug at different times, the response time may vary considerably from dose to dose. Bayer scientists noticed these intra- and inter-individual bioavailability differences in practice in their studies on beagles and women. This presented a further complication because Bayer required the drug to be 99% effective, and work on all women at a single dose—"one dose must fit all." A normal pill may not present such variations, but will expose its contents to the stomach's highly acidic environment.

Dr. Johannes Tack, a Bayer scientist, began work in 1983 to develop drospirenone into an oral contraceptive. At the time, Bayer had been working with a related compound, spirorenone, as a diuretic. When consumed, spirorenone metabolizes into drospirenone, which is still a diuretic, but was found to have progestogenic (contraceptive) effects. Spirorenone itself had some contraceptive effects that Bayer concluded were the result of the appearance of drospirenone when it metabolized. Bayer decided to harness the diuretic effect of isolated drospirenone to create the new contraceptive. Tack consulted prior Bayer work with drospirenone including in vitro isomerization studies performed by a fellow Bayer scientist, Dr. Werner Krause. Krause had also performed in vivo studies with spirorenone, about which he published three articles. These studies, Krause I, II, and III, included the knowledge that drospirenone was a metabolite of spirorenone. Tack decided, however, that these in vivo studies garnered little information on the practice of drospirenone in vivo.

Tack tested the stability of drospirenone in acid at pH 1 to simulate the conditions of the stomach. He

found that after 10 minutes, 21% of the drospirenone had isomerized in the acid, and after 45 minutes, half had isomerized. He came to a critical conclusion:

> If the results obtained in vitro are applied to in vivo conditions, it can be presumed that, with an assumed gastric juice volume of 100ml, the majority of the dose (solubility of drospirenone 5-10 mg/l) passes into solution during passage through the stomach and consequently undergoes rapid isomerization. A clear reduction in the bioavailability of the unchanged active substance is to be expected as a result.
>
> The planned studies on the progestogenic efficacy of [drospirenone] should therefore be performed with an enteric-coated formulation.

Tack then moved into clinical studies with an enteric-coated formulation of drospirenone. For five years, Bayer used this coated pill in its studies, even reconfirming in 1988 that drospirenone needed an enteric coating because it isomerized quickly in a pH 1 acidic solution.

In 1988, Bayer also planned a study to determine how effectively its enteric-coated tablet delivered a formulation as compared to an intravenous injection of the same formulation. This study would thus measure the "absolute bioavailability" of the drug. Bayer added what it terms a "non-routine" element to the study, by which it added an unprotected (normal) drospirenone tablet and compared its bioavailability to that of the enteric-coated formulation and the intravenous delivery. Tack expected to find that the enteric-coated tablet would produce a lower bioavailability than an intravenous injection, while the normal pill would produce an even lower bioavailability than the enteric-coated tablet. However, he found

that despite his observations that drospirenone would quickly isomerize in a highly acidic environment and his belief therefore that an enteric coating would be necessary to preserve bioavailability, the normal pill and the enteric-coated pill resulted in the same bioavailability. Following this study, Bayer developed drospirenone in a normal pill, for which it would eventually receive the '531 patent.

Bayer relied on the finding that drospirenone would absorb with a normal pill to overcome an obviousness rejection in the Patent and Trademark Office. During prosecution, the examiner rejected the claims as obvious in view of a De Castro reference, which the examiner said taught to micronize poorly soluble drugs to increase their bioavailability. Bayer responded that another piece of prior art, the Nickisch reference, taught that micronizing drospirenone would increase its exposure to the highly acidic environment in the stomach, which would result in increased isomerization. The examiner allowed the claims, giving the specific reason that the prior art suggested that micronizing drospirenone would not work: "The micronized drospirenone will be degraded even more rapidly because the micronization of drospirenone expose [sic] the drug particles in the stomach (acidic). Therefore, to formulate an oral dosage forms [sic] containing the drospirenone particles, which exposed to the gastric environment upon dissolution, would be un[o]bvious in view of the data presented . . . . "

The '531 patent issued on September 7, 2004. Claim 1 is representative:

1. A pharmaceutical composition comprising

from about 2 mg to about 4 mg of micronized drospirenone particles, about 0.01 mg to about

0.05 mg of 17.alpha.-ethinylestradiol, and one or more pharmaceutically acceptable carriers,

the composition being in an oral dose form exposed to the gastric environment upon dissolution,

and the composition being effective for oral contraception in a human female.

Barr Laboratories ("Barr") makes generic pharmaceuticals, and filed an Abbreviated New Drug Application with the Food and Drug Administration seeking approval to market a generic version of Yasmin®. Bayer promptly filed a patent infringement suit against Barr. The parties agreed that if the '531 patent is valid, Barr infringes claims 1, 5, 8, 27, 29, 36, 49, and 50. Barr then alleged that these claims are obvious, among other invalidity and unenforceability arguments. At trial, the two parties agreed that 2-4 mg drospirenone was well known in the art, as well as its combination with 0.01-0.05 mg 17 α-ethinylestradiol, a pharmaceutically acceptable carrier, and a kit containing 21 such tablets with active ingredients and 7 placebos, to be used as an effective oral contraceptive in human females. Bayer claimed that its innovation was that the drospirenone could be micronized to increase its bioavailability, and that the micronized drospirenone would not need to be enteric coated for protection against the highly acidic gastric environment.

The district court ruled that these claims were invalid as obvious, and rejected Barr's other theories. The court found that a person having ordinary skill in the art would have considered the Krause I, II, and III studies' results that spirorenone though acid-sensitive would nevertheless absorb in vivo because drospirenone is closely related to spirorenone. It also

found that while the Nickisch reference did teach that drospirenone isomerizes in vitro when exposed to acid simulating the human stomach, a person of ordinary skill would be aware of the study's shortcomings, and would verify whether drospirenone absorbed or isomerized with precise in vivo and in vitro testing as suggested by the Robert Aulton treatise, Pharmaceutrics: The Science of Dosage Form Design (1988). It then held that under *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007), it would have been obvious to a person having ordinary skill in pharmaceutical formulation to try a normal pill in formulating drospirenone as an oral contraceptive. Bayer timely appeals this ruling; Barr does not cross-appeal its adverse rulings. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

Obviousness under 35 U.S.C. § 103 is the sole issue in this appeal. Whether an invention would have been obvious at the time the invention was made is a question of law, which we review *de novo*, based on underlying facts, which we review for clear error. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1355 (Fed.Cir.2007). A district court's finding is clearly erroneous when, despite some supporting evidence, we are "left with the definite and firm conviction that a mistake has been committed." *Forest Labs., Inc. v. Abbott Labs.*, 339 F.3d 1324, 1328 (Fed.Cir.2003) (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 92 L.Ed. 746 (1948)).

A patent may not be obtained if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. § 103(a). An obviousness analysis is based on several factual inquiries. A court must examine the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). At that point, a court may consider secondary objective evidence of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, and the like. *Id.*

In *KSR*, the Supreme Court stated that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421, 127 S.Ct. 1727. This approach is consistent with our methodology in *In re O'Farrell*, 853 F.2d 894 (Fed.Cir.1988). *See Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed.Cir.2009); *In re Kubin*, 561 F.3d 1351, 1359, (Fed.Cir.2009). *O'Farrell* observed that most inventions

that are obvious were also obvious to try, but found two classes where that rule of thumb did not obtain.

First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir.2008).

Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Because the use of drospirenone with 17 α-ethinylestradiol as an oral contraceptive was known prior art, Bayer represented that the innovation was to micronize the drospirenone to increase its bioavailability, and that the micronized drospirenone would absorb with a normal pill, against the teachings of the prior art. The district court analyzed the prior art and determined that micronizing drospirenone was taught, and that using a normal pill would have been obvious to try.

The court first determined how the person having ordinary skill in the art of pharmaceutical formulation would consider the correlation of in vitro and in vivo tests. It relied principally on Robert Aulton's pharmacologist textbook, Pharmaceutics: The Science of Dosage Form Design, which, as the court found, teaches that "dissolution rate data when combined with solubility . . . provide an insight to the formulator into the potential in vivo absorption characteristics of a drug. However, in vitro tests only have significance if they can be related to in vivo results. Once such a relationship has been established, in vitro dissolution tests can be used as a quality control test. (Aulton, p. 9)." The court concluded that the person of ordinary skill would not accept in vitro testing as valid without a correlation to in vivo tests.

With that knowledge, the court then turned to micronization. It found that Aulton cut both ways on this point, because it taught both that micronizing a poorly water soluble substance like drospirenone may increase its absorption rate, but may also increase the rate of degradation. However, Aulton stated, and other evidence corroborated, that "it is now generally recognized that poorly soluble drugs showing a dissolution rate limiting step in the absorption process

will be more readily bioavailable when administered in a finely subdivided [micronized] form with larger surfaces than as the coarse material . . . . The fine material often in micronized form with larger specific surface dissolves at faster rates which can lead to improved drug absorption by passive diffusion." The district court acknowledged that the prior art suggested that there would be concern about the dissolution of a poorly water soluble acid-sensitive drug, but found that the prior art generally suggests that micronization could improve the dissolution of drospirenone. It concluded that a person having ordinary skill would have seen it as a viable option.

Bayer argues that this is clear error because the court relied on one piece of prior art to show that micronization has been shown to work on acid-sensitive compounds. The court reviewed the Hargrove reference, which was a study on micronizing progesterone, concluding that "it confirms that not all acid-sensitive drugs require enteric coating." This is incorrect, as Barr agrees, because progesterone is not an acid-sensitive drug. However, Bayer's own expert, Dr. James McGinity, testified that micronization is the first choice solution because it presents the best chance for success. So there remains adequate support for the conclusion that micronization was a viable option.

The district court then moved to Bayer's second alleged non-obvious aspect of the invention, whether the formulation should use an enteric-coated or normal tablet delivery. The court considered Bayer's argument that prior art taught formulation scientists to employ an enteric coating on drospirenone, and Barr's argument that an enteric coating is so complicated, expensive, cumbersome to manufacture, and

prone to variability that it only would be used as a last resort by formulation scientists working with an acid-sensitive drug. The court found neither side persuasive, and considered the prior art as the center, again focusing on the Aulton textbook. It found that Aulton recognizes the necessity of an enteric coating to the formulation of acid-sensitive drugs, but that an enteric coating also introduces drawbacks, including that enteric coated tablets have the lowest bioavailability of all drug delivery forms. Poor bioavailability of drospirenone is the major problem that Tack sought to solve. The district court further found that Aulton teaches that there is variability in bioavailability both intra- and inter-subject when using enteric coated tablets, which is a significant obstacle to Bayer's requirement that the drug must be 99% effective for all women.

In effect, while Bayer argued that prior art teaches away from using micronized drospirenone in a normal tablet, Barr argued that the prior art teaches away from using an enteric coating. What the parties have done, however, is present the options available to a pharmaceutical formulator having ordinary skill to solve the problem of acid-sensitive but hydrophobic drospirenone.

Barr argued that the Krause series on spirorenone is controlling because of the great similarity between spirorenone and drospirenone. The Krause series tested the bioavailability of spirorenone in vivo in humans and monkeys to determine whether there was need to develop a "pharmaceutical formulation resistant to gastric juice." The studies each found no spirorenone isomers in the subjects' blood streams, and concluded that spirorenone is absorbed before it isomerizes. Furthermore, an in vitro comparison found that dros-

pirenone isomerized in pH 1 acid with a profile similar to spirorenone. The court found that the drugs were closely related in that they are both (1) acid-sensitive at similar rates, (2) steroids having the same pharmacological properties, (3) derivatives of the same drug, (4) of the same chemical composition except for one bond, and (5) from the same family of substances. The court then concluded that a person of ordinary skill would find the drugs closely related, and would therefore access these studies when formulating drospirenone. He would be led to believe that drospirenone, like spirorenone, may absorb in vivo, but isomerize in vitro.

Bayer argues now that the district court ignored key differences between drospirenone and spirorenone, such as that the former isomerizes 40% faster than the latter, and that drospirenone is more soluble and thus could dissolve and isomerize in acid faster. This is irrelevant because the Krause series prior art is not an anticipatory reference. It can be used to show that a drug formulator having ordinary skill had a viable known option to consider with micronized, unprotected drospirenone, and a reasonable expectation that drospirenone would perform similarly (even if not identically) to the spirorenone in the Krause series. *See O'Farrell*, 853 F.2d at 903-904 ("Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success.").

Similarly, Bayer argued that the Nickisch article teaches that drospirenone isomerizes when exposed to acid in vitro, teaching away from allowing exposure to the gastric environment, and thus suggesting the need for an enteric coating. Barr attacked the merits of the study as it would apply to the practice of

drospirenone in vivo, noting that Nickisch did not test drospirenone in vivo to correlate its in vitro findings. Barr also challenged the Nickisch reference on the grounds that drospirenone was found to isomerize slowly and would not have isomerized before the stomach emptied, that the in vitro environment was too extreme to be compared to an in vivo practice, and that it did not explain its testing protocols. The court found that a person of ordinary skill in the art would recognize that Nickisch establishes that drospirenone isomerizes in vitro, but would be alerted to the study's shortcomings when used in vivo.

At this point, a person having ordinary skill in the art has reached a crossroads where he must choose between two known options: delivery of micronized drospirenone by a normal pill following the spironenone analogy in the Krause series, or delivery of drospirenone by an enteric-coated pill following the Nickisch teaching that the drug needs to be protected from the stomach. This is a finite number of identified, predictable solutions. *See KSR*. 550 U.S. at 421, 127 S.Ct. 1727. The prior art would have funneled the formulator toward these two options; he would not have been required to try all possibilities in a field unreduced by the prior art, thus avoiding the first pitfall of *O'Farrell*, 853 F.2d at 903. Additionally, the prior art was not vague in pointing toward a general approach or area of exploration, but rather guided the formulator precisely to the use of either a normal pill or an enteric-coated pill, thus avoiding the second pitfall of *O'Farrell*. *Id*. Because the selection of micronized drospirenone in a normal pill led to the result anticipated by the Krause series, the invention would have been obvious. *See KSR*, 550 U.S. at 421, 127 S.Ct. 1727.

CONCLUSION

Accordingly, the judgment of the United States District Court for the District of New Jersey is affirmed.

AFFIRMED

NEWMAN, *Circuit Judge*, dissenting.

With all respect to my colleagues, I do not share their view that it would have been obvious to do that which was indisputably unobvious to the experienced formulation scientists whose assignment was to formulate the known product drospirenone. The evidence showed, without contradiction, that it was known that micronized drospirenone rapidly degraded at the acidity of stomach acid. The evidence showed, without contradiction, that the Bayer scientists working in this field believed that the product required an enteric coating in order to prevent degradation in the stomach, upon ingestion as an oral contraceptive. Yet my colleagues, employing their own expertise, hold that since the scientists working in this field turned out to be mistaken, it would have been obvious that it was not necessary to take steps to prevent acid degradation. The court discounts the testimony of the scientists themselves, ignores the knowledge concerning this product and its instability in acid, ignores the textbook teachings, and finds that this unlikely process obviously should have been tried. That is not the law of obviousness.

The statutory criterion is whether the invention would have been obvious to persons of ordinary skill at the time of the invention, not whether it is sufficiently simple to appear obvious to judges after the discovery is finally made, despite the years of contrary belief among the scientists charged with the

project. At the time that the Bayer scientists were attempting to formulate drospirenone as an oral contraceptive, the textbook teaching was that micronizing acid-sensitive products would accelerate their acid-induced degradation. *See, e.g., Aulton's Pharmaceutics: The Design and Manufacture of Medicines* (advising against micronizing acid-sensitive drugs because it reduces the drug's bioavailability). My colleagues criticize these specialists, and rule that it was nonetheless obvious to conduct experiments that they believed would not work. The court rules that the scientists should have "tried" that which they believed would fail, and that when they eventually did try this unlikely formulation, and it succeeded, it was obvious to do so.

The unusual physiological behavior of drospirenone in the stomach was not known; this knowledge followed as scientific explanation; it did not precede the invention in suit. There was no evidence to reasonably suggest that micronized drospirenone was likely to be usable, with 99+ percent consistency of effectiveness, without any protection from degradation by stomach acid. A usable contraceptive requires virtually complete effectiveness, and the standard confronting the Bayer scientists was high. Unlike the unrelated drugs cited by the panel majority, contraceptives require complete effectiveness. Previously known oral contraceptives such as progesterone and spironolactone are not acid sensitive, and drospirenone presented a highly specific challenge to the formulation scientists. The Bayer scientists believed that the way of avoiding the known acid degradation of drospirenone was to protect it from acid. My colleagues, however, find that it would have been obvious to expose it to acid, although it was not obvious to the scientists working on the project.

"Obviousness" requires that the subject matter was obvious to persons of ordinary skill in the field of the invention. The law does not hold it "obvious to try" experiments that contravene conventional knowledge, and that are not deemed reasonably likely to succeed. The evidence in this case is a better measure of obviousness than is the hindsight science of judges, for the scientists who eventually made this discovery testified, without dispute, that they did not believe an uncoated micronized product would meet the demanding criteria of contraceptive effectiveness. The Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) explained that the standard for "obvious to try" is whether there was a "reasonable expectation of success" at the time. It was undisputed that there was not. It was undisputed that it was not reasonably expected that uncoated micronized drospirenone would be 99+% effective as an oral contraceptive when ingested into the acidic stomach, when it was known to degrade rapidly in acid.

The district court stated that micronization was a "viable" option, and that although success was "uncertain," the invention was obvious to try. However, "viability" is not the standard. "Viability" implies that the experiment may or may not succeed. What the law requires is not guesswork, not dumb luck, but a reasonable degree of predictability of success. My colleagues depart from the statutory standard, in ruling that persons of ordinary skill would have conducted experiments that were expected to fail. Nothing in the prior art teaches the likelihood of success of ingestion of uncoated micronized drospirenone; what is taught is the likelihood of failure.

The invention must be viewed as a whole. With the existing knowledge that drospirenone is both hydrophobic and that it degrades rapidly in acid, and the existing knowledge that micronization, although useful to counteract a drug's hydrophobic properties, renders the drug even more susceptible to acid degradation, it was not shown that a person of ordinary skill in this field would have had a reasonable expectation of achieving complete contraceptive bioavailability and effectiveness with uncoated micronized drospirenone. The contrary view has surfaced only in this litigation-induced argument. The exercise of judicial expertise to override the clear evidence of how persons of skill in this field actually behaved, is inappropriate.

I respectfully dissent.

APPENDIX B

UNITED STATES DISTRICT COURT
D. NEW JERSEY

Civil Action No. 05-cv-2308 (PGS)

BAYER SCHERING PHARMA AG and
BAYER HEALTHCARE PHARMACEUTICALS INC.,
Plaintiffs,

v.

BARR LABORATORIES, INC.,
Defendant.

March 3, 2008.

OPINION

SHERIDAN, District Judge.

Pursuant to the Hatch Waxman Act, Bayer Schering Pharma AG[1] ("Bayer") brings this action to (1) declare that its patent of an oral contraceptive (Def. 17 at p. 6) marketed as Yasmin® is valid; and (2) to enjoin Barr Laboratories' ("Barr") generic version from proceeding to market.[2] The patent in question is entitled "Pharmaceutical composition for use as a contraceptive" bearing U.S. Patent No. 6,787,531

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[1] Over the last twenty years, plaintiff's corporate ownership has changed. This is not an issue here. Throughout this Opinion, plaintiff is identified as "Bayer."

[2] Barr presently has an "abbreviated new drug application" ("ANDA") pending before the U.S. Food and Drug Administration ("FDA").

("'531 Patent"). The Court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

The complaint was filed in April 2005, and there was significant discovery undertaken. On November 13, 2007, a final pretrial order was entered which limited the issues to be tried. Barr contends the '531 Patent is invalid because (1) the asserted claims would have been obvious to a person of ordinary skill in the art (Def. 18 at p. 7); (2) the claimed invention was publicly used in the United States prior to the Critical Date of the '531 Patent (Def. 6 at p. 6); and (3) persons involved in the prosecution of the '531 Patent committed inequitable conduct. The trial was conducted from November 15, 2007 through December 4, 2007. On December 21, 2007, the parties submitted proposed findings of fact and conclusions of law.

For organizational purposes, the Court subdivides this Opinion into the following sections: Introduction, Glossary of Terms, Witnesses, Chronology of Events and Statement of Facts, Assessment of the Invention Development Path Evidence, Obviousness, Prior Public Use, Inequitable Conduct, and Conclusion.

I.

INTRODUCTION

Generally, drug formulators are confronted with the problem of determining a drug dose form so that it dissolves, absorbs into the bloodstream, and becomes bioavailable for its intended purpose. Often the physical properties of the drug complicate the formulation of a drug. This is the case here.

The claimed invention is an oral contraceptive. It is comprised of a combination of drugs (drospirenone

and ethinylestradiol) (Def. 8 and 9 at p. 5) that are micronized (Def. 16 at p. 6) and delivered in an immediate release tablet.[3] Bayer argues that this formulation is unique because drospirenone is acid sensitive and poorly water soluble. According to Bayer, since drospirenone isomerizes (Def. 14 at p. 6) or degrades in pH 1 hydrochloric acid (a condition that may exist in the stomach), the prior art teaches away (Def. 22 at p. 7) from micronizing and immediately releasing drospirenone. That is, prior art warns that micronizing an acid-sensitive drug such as drospirenone and exposing it to stomach acid may lead to unacceptable levels of degradation. As a consequence, the person of ordinary skill in the art would be taught to avoid dissolving drospirenone in stomach acid, and would instead protect it by applying an enteric coating (Def. 10 at p. 5) so that it can dissolve in the duodenum, which is a far less acidic environment. The claimed invention is that, in the face of this prior art, Bayer exposed drospirenone to stomach acid without a coating, and micronized it to increase dissolution (Def. 7 at p. 6) in the stomach.

Barr contends there is nothing new about the claimed invention. More specifically, micronization (Def. 16 at p. 6) and enteric coatings are ordinary

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[3] Specifically, the suit seeks to determine whether the asserted claims, which include claims 1, 5, 27, 36 and 49 (composition claims), and claims 8, 29, 36 and 50 (kit claims) violate the doctrines of obviousness, prior public use or inequitable conduct. With regard to obviousness, the parties concede that the outcome of the inquiry is based on the non-enteric coated micronized drospirenone/ethinylestradiol combination. (Bayer's Proposed Findings of Fact at ¶¶ 210-11; Barr's Response to Bayer's Proposed Findings of Fact at ¶¶ 210-11). Therefore, if these claims fail for obviousness, then all the asserted claims will fail for obviousness.

drug formulation techniques, like arrows in the quiver of a bowsman, that have been known in the art for decades, and are routinely considered by formulators when determining how to maximize absorption (Def. 1 at p. 4) of a drug and bioavailability (Def. 5 at p. 4). In addition, Barr argues that since the formulation had already been reduced to practice in Europe prior to the start of the U.S. clinical trial, this constituted a prior public use that occurred more than a year prior to the filing of the patent application. In support of this argument, Barr argues that Bayer figured out how to formulate the claimed invention in 1988 in Germany. Then, after numerous clinical trials in Europe, Bayer commenced a clinical trial in the United States sometime prior to August 31, 1998. Bayer refutes this contention by arguing that the clinical trials were experimental in nature and exempt from the public use bar. Lastly, Barr argues that two agents of Bayer (Drs. Ellman and Lipp) submitted false or misleading information to the Patent Office during the '531 Patent prosecution, which would constitute inequitable conduct. According to Barr, Dr. Ellman failed to disclose the voluminous European clinical trial history, which may have effected the patent examiner's view of the public use bar. Additionally, Dr. Lipp allegedly mischaracterized the prior art concerning the acid sensitivity of drospirenone compared to other forms of drugs when he submitted a declaration to the patent examiner. Bayer generally denies these allegations. Each of these issues are discussed at length below.

II.

GLOSSARY OF TERMS

There are certain scientific words that are used repeatedly throughout the Opinion. For the sake of

consistency, and to avoid dispute, these words are defined as they will be used.[4]

1. Absorption means the process by which an active ingredient enters the bloodstream (3T 78, 21-25).

2. Agglomeration occurs when smaller particles aggregate together to form a larger particle (2T 84, 2-7).

3. Aldosterone antagonist means antimineralocorticoid effect. It is a property of a drug which prevents or lessens water retention in a living being (Heithecker Dep. 49, 18).

4. Anti-androgenic effect means a property of a drug which reduces or eliminates acne. Dr. Heithecker explained it plainly: "it avoids pimples on your face." (Heithecker Dep. 71, 24).

5. Bioavailability means the amount of the active ingredient that is available to act on the body (3T 78, 15 through 79, 7; 4T 41, 15-17).

6. Critical Date of the '531 Patent is August 31, 1998. An invention is not patentable if it was "in public use . . . in this country, more than one year prior to the date of the application for the patent in the United States." Any use outside of the United States is not a "public use . . . in this country." 35 U.S.C. § 102(b).

7. Dissolution is a process by which drug particles are solubilized by the fluids at some point along the gastrointestinal tract[5] (PTX 11; Aulton 1988 at 8-9).

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[4] For the first several times a glossary term is used in the text, its definition cite is provided.

[5] Dr. Chambliss described dissolution as taking a glass of iced tea and adding granular sugar—you have to stir vigorously to

A drug molecule must be dissolved before it can be absorbed (1T 41, 25 through 42, 2; PTX 11, Aulton 1988 at 3).

8. Drospirenone (aka 1,2-dihydro-spirorenone) is a poorly water soluble, acid-sensitive steroid. It is a metabolite of spirorenone. It has three chief pharmacological properties. First, drospirenone is a progestin, which enables it to inhibit ovulation (PTX 100; JX 9). Second, drospirenone is an antimineralocorticoid, which gives it a diuretic or anti-bloating effect (PTX 100; JX 17 at 109). Third, drospirenone is an anti-androgen, which means it can prevent acne (3T 130, 10-18; 6T 69, 19-23).

9. Ethinylestradiol is an orally active synthetic derivative of estradiol, a female sex hormone (1T 22, 19-21).

10. Enteric coating means a pH-sensitive film applied to a tablet[6] (1T 54; 5-12). An enteric coating dissolves only after the tablet empties from the stomach and reaches the higher pH (less acidic) environment of the duodenum (7T 22, 14-20). Formulators use enteric coatings for two purposes: to protect a drug from degrading in the acidic environment of the stomach, and to prevent stomach irritation (7T 24, 15-22; PTX 19 at 171; PTX 184 at 1943).

11. In vitro study is a laboratory test which simulates body conditions (1T 11, 23 through 12, 8; 5T 24, 8-13, 21 through 25, 25; 1T 63, 17-18).

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get the sugar into solution; but if confectionary powder is added to the iced tea, little stirring is required because the particle size is smaller (1T 40, 15-19).

[6] Dr. Chambliss compared enteric coating to "Saran Wrap, a film . . . that will not open up" readily (1T 54, 8).

12. In vivo study means tests performed on living animals or humans (1T 63, 19-23).

13. Isomers are molecules that have the same molecular formula and molecular weight, but differ in their connectivity pattern or three-dimensional spatial arrangement; isomers may be biologically active or inactive (3T 77, 3-8).

14. Isomerization is a specific type of molecular degradation (3T 77, 9-13).

15. Metabolite means a chemical product derived from the breakdown (metabolism) of another chemical; it may be biologically active or inactive (7T 142, 9-14; 5T 70, 4-13, 7T 47, 11-13).

16. Micronization is a formulation process whereby a drug particle is reduced in size, thus increasing its available surface area in order to increase the dissolution rate of the drug (1T 40, 12-19; 7T 13, 12-19; 7T 63, 4-6; see Chaumeil, DX 461, at 213; McInnes, JX 19 at 415; Fotherby, JX 20 at 61).

17. Oral Contraceptive is a pharmaceutical in tablet form taken orally by females that prevents pregnancy by inhibiting ovulation, thickening cervical mucus and affecting sperm capacitation (9T 9, 25 through 10, 9; 9T 57, 2-5). It usually contains a progestin and estrogen component (9T 9, 15-21). Generally, a commercially viable oral contraceptive must be 99% effective and must have one uniform dose (9T 10, 12-16; 11, 4-13).

18. Person of ordinary skill in the art is a hypothetical person, who at the time of the invention, has either (1) a Ph.D. in a field related to pharmaceutical formulation and processing (such as physical chemistry, medicinal chemistry, or pharmaceutics) or (2) a similar undergraduate degree and at least several

years of experience in formulation (1T 30, 14-22; 6T 60, 14-22).

19. Solubility means the amount of a compound that can dissolve in a given volume of liquid (7T 95, 3-21).

20. Spironolactone is a diuretic and can be used as an antiandrogen. (JX 19, McInnes at 410; DX 1038 at 546). An antiandrogen is a compound that is capable of preventing or inhibiting the biological effect of male sex hormones (JX 17, Muhn 1995 at 104).

21. Spirorenone is an acid-sensitive steroid with a similar structure to drospirenone but for one chemical bond, and has certain pharmacological properties that are similar to those of drospirenone. Spirorenone does not itself act as a progestin in humans. Rather, spirorenone metabolizes into drospirenone when taken by humans (PTX 211 at SBPL 02295588; 1T 69, 5-16).

22. Teaching away is when the person having ordinary skill, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994).

23. Therapeutic indication means the purpose for which a pharmaceutical product is intended. That is, the use to which such a product will be put clinically (3T 132, 12-19; 4T 42, 23 through 43, 4).

III.

WITNESSES

There were a number of expert and fact witnesses who testified at trial or whose video deposition was submitted. These witnesses shall be referred to

throughout the Opinion. As such, the Court briefly sets forth their backgrounds.

Bayer Expert Witnesses:

* James McGinity, Ph.D. is an expert in pharmaceutics and formulation science (6T 59, 5 through 64, 9). He performed his undergraduate work at University of Queensland, Australia and earned his doctorate from the University of Iowa. He is a Professor of Pharmacy at the University of Texas. Dr. McGinity also serves as a consultant for several chemical and pharmaceutical companies. He functions as a peer reviewer for 15 journals, is on the editorial advisory board of 10 pharmaceutical journals, and has significant experience with enteric coatings.

* Lee Shulman, M.D. is an expert witness qualified to offer expert opinions on the effectiveness, the side effects, profile, and clinical trials of oral contraceptives (9T 3, 1 through 9, 11). He earned his undergraduate degree and graduate degree in medical education from Cornell University. He is Diplomat of Obstetrics and Gynecology, Diplomat of Medical Genetics, and Professor of Obstetrics and Gynecology at Northwestern University, Chicago. Dr. Shulman is a practicing physician. He is currently completing his term as Chairman of the Board of Trustees of the Association of Reproductive Health Professionals. He has received numerous awards for his work, served on numerous editorial boards, and authored over 40 peer-reviewed articles.

* Larry Nixon, Esq. is an expert in patent law and practice (PTX 0029; 8T 84, 4 through 87, 2). He has an undergraduate degree and masters degree in electrical engineering from the University of Illinois. He earned his law degree from Georgetown in 1971.

He is a registered patent attorney and has practiced for more than 35 years. He is a frequent lecturer and has published several articles on patent practice.

Bayer Fact Witnesses:

* Johannes Tack, Ph.D. is a fact witness who explained the claimed patent's internal development path. He is a named inventor of the '531 Patent. Most of his undergraduate studies were from University of Bonn in Germany. After he received his doctorate, he joined Bayer. After 21 years with the company, he left and formed Axxons, a spin-off of Bayer, where he is developing drugs to treat neurodegenerative diseases such as Parkinson's Disease (5T 46, 14 through 54, 21).

* Herman Ellman, M.D. was a fact witness on clinical trial practices in the United States of various drugs, including the claimed invention. He received his medical degree in 1972 from Columbia University. Dr. Ellman worked for Bayer from 1980-2000 where he solely focused on the planning and overseeing of clinical trials of various drugs (8T 3, 5 through 5, 9).

Barr Expert Witnesses:

* Walter G. Chambliss, Ph.D. is an expert in the formulation of drugs and dosage form design (1T 7, 7 through 15, 6). He is presently a Professor of Pharmaceutics at the University of Mississippi. He is also currently Director of Technology Management and a research professor in the National Center for Natural Products Research at the University of Mississippi. Dr. Chambliss received his undergraduate degree, masters degree, and doctorate, all in pharmaceutics, from the University of Mississippi. He has had a distinguished 27-year career in the private sector including holding the position of Vice

President of Pharmaceuticals Research and Development at Schering-Plough, as well as spending time with G.D. Searle and Bristol Myers. He has authored a book and many articles on pharmaceutics generally, and specifically, on enteric coatings.

* Yoshada Pramar, Ph.D. is an expert in pharmaceutical formulation (5T 15, 18 through 18, 1). She obtained her undergraduate and her masters degree from the University of Baroda, India, and she earned her doctorate from the University of Houston. Since 1991, she has been a Professor of Pharmaceutics at Xavier University and has consulted on the formulation of oral contraceptives. She is a member of three professional pharmaceutical associations and has published over 30 articles in scholarly journals (DX 421).

* Bhagu Bhavnani, Ph.D. is an expert in sex steroids (3T 122, 11 through 125, 23). He has an undergraduate degree in chemistry and his post-graduate bachelor's degree in technology of pharmaceuticals, both from Bombay University (DX 406). He received his masters and doctorate in pharmacy from University of Massachusetts College of Pharmacy and Worcester Foundation for Experimental Biology. He is a professor at the University of Toronto in the Department of Obstetrics and Gynecology and is a scientific research director at St. Michael's Hospital in Toronto. He has more than 40 years experience in "steroid hormones."

* Gerald J. Mossinghoff is an expert in the field of Patent Office rules and procedures (4T 64, 21 through 71, 9). He has a bachelor of science from St. Louis University and his law degree from George Washington University. He is senior counsel in the firm of Oblon, Spivak, McClelland, Maier & Neustadt.

He lectures at George Washington University Law School. He is a member of the Intellectual Property Hall of Fame. His distinguished career includes time as a patent examiner, Director of the Office of Legislative Planning, Assistant Secretary of Commerce, and Commissioner of Patents and Trademarks.

Barr Fact Witnesses:

* Renate Heithecker, Pharm. D. is an employee of Bayer. Portions of her video deposition were submitted into evidence. She earned a degree in pharmacy from the Technical University in Berlin in 1971. She has held numerous positions over the years at Bayer or its predecessors, including research associate, head of a group known as Contraception and Clinical Research, specialist pharmacist for medical education, and head of a group known as Medical Affairs Europe, Gynecology and Cardiology (Heithecker Dep. 25, 34:7-34:9).

* Ralph Lipp, Pharm. D. is a former employee of Bayer. Portions of his video deposition were submitted into evidence. He attended the University of Mainz where he earned a degree in pharmaceutical studies, and thereafter studied in Weitersladt. He was a researcher in a unit of the Free University called Instrumental Analysis and Drug Formulation, focusing on medicinal chemistry. In the 1990s, he held several positions with Bayer, including head of a group named Drug Delivery Systems-Transdermal Systems. Dr. Lipp has also been head of Bayer groups known as Oral Dosage Forms and Pharmaceutical Development. Today, Dr. Lipp is the Executive Director of Pharmaceutical Sciences Research and Development at Eli Lilly (Lipp Dep.10:10-10:15).

IV.

CHRONOLOGY OF EVENTS AND STATEMENT OF FACTS

Since the 1970s, drug formulators have developed many techniques to increase the bioavailability (Def. 5 at p. 4) of orally administered drugs. Two of these proven techniques are enteric coatings (Def. 10 at p. 5), and micronization (Def. 16 at p. 6). Depending on the physical characteristics of a drug, these techniques may or may not be employed by the formulator. With regard to the formulation of oral contraceptives on the market in the 1970s, micronization was used, but enteric coating was not.

In 1978, the World Health Organization recommended that oral contraceptive research focus on the development of products containing the lowest possible doses of estrogen and progestin due to health risks associated with those steroids. Since the use of progestins is linked to cardiovascular disease, reducing the progestin use may "lower the risk of cardiovascular complications such as stroke and ischemic heart disease." (DX 055).

Also that year, Bayer obtained a patent entitled "Spirolactone" bearing U.S. Patent No. 4,129,564 ("Spirolactone Patent") (Def. 21 at p. 7) with drospirenone (Def. 8 at p. 5) as a claim (DX 50).

1. *Internal Development Path of the '531 Patent*

Also in 1978, Dr. Johannes Tack, an inventor of the '531 Patent, completed his doctorate degree in pharmacology, (see p. 9 for a brief biography) and commenced his career with Bayer as a product manager in its marketing department (5T 49, 4-5). Two or three years later, Tack transferred to the

pharmakenetics department, and then in 1982, Dr. Tack was assigned to the galenics (formulation) department.

In 1982-83, Dr. Krause of Bayer conducted an in vitro/in vivo study (Def. 11 and 12 p. 6) of spirorenone (Def. 21 at p. 7). His articles, referred to as Krause I, II, and III, are discussed throughout this Opinion. In April 1983, Bayer alleges that it faced a significant strategic decision to determine whether to pursue development of spirorenone or drospirenone, so it held a strategic meeting with many of its renowned scientists, including but not limited to, Hümpel, Lachnit, Losert, Krause, Nickisch, and Tack (PTX 211). Although the minutes of that meeting do not precisely reflect it, the issue was whether Bayer should allocate resources for development of a diuretic (spirorenone [)] (Def. 21 at p. 7) or an oral contraceptive (drospirenone). At the meeting, Bayer decided to pursue development of drospirenone since it has aldosterone antagonist properties (Def. 3 and 4 at p. 4), which may ameliorate symptoms of congestive heart failure (5T 66, 22-25). During the course of the strategic meeting, Krause reported on his kinetic studies in vitro/in vivo (Def. 11 and 12 at p. 6) regarding spirorenone (PTX 211). He cautioned his colleagues that his studies were with spirorenone and "little information could therefore be presented in practice on" drospirenone. However, the conclusions of the group as a whole suggest that the research of Krause was of some benefit. The minutes of the strategic meeting state in pertinent part:

> Rationale for the selection of ZK 30 595 (drospirenone) for clinical trial (phase I):
>
> The kinetic studies in humans mentioned in 2) above provided clear indications that spirorenone

had been transformed to a significant degree into [drospirenone], and the metabolite must consequently be responsible for the progestogenic action of spirorenone (it lead [sic] to the termination of other trials in the CV indication).

In the opinion of Dr. Schuppler, toxicological studies with [drospirenone], particularly systemic studies of >4 weeks' duration (p.o.) are therefore unnecessary, since the plan for the time being is to demonstrate progestogenic action (see below) with a maximum administration period of 21 days. The tolerability data from the 14 day human study with spirorenone (highest tested dosage = 40 mg/day p.o.) are sufficient as a basis for this, as they include testing of the metabolite [drospirenone] formed in the body from spirorenone in sufficiently large quantities (approx. 8-10 mg/day).

(PTX 211).

As a result of the meeting, Dr. Tack was assigned the task of formulating 1 mg drospirenone tablets for use in small clinical trials to assess ovulation inhibition (PTX 211). It was one of his first assignments in the galenics department (5T 52, 7-10). Over the next several months, Dr. Tack undertook his assignment on the development of a tablet. In September, 1983, Dr. Tack conducted in vitro tests of drospirenone. By exposing drospirenone to hydrochloric acid, he found that after 10 minutes, 21% of the drospirenone had been transformed into its isomer (Def. 13 at p. 6); and after 45 minutes, half the dose had isomerized. Since hydrochloric acid has a pH level of 1, it is roughly similar to the gastric juices of the stomach. Tack concluded that the majority of the drospirenone dose (2 mg to 4 mg) would dissolve in the stomach and

undergo rapid isomerization (Def. 14 at p. 6). This would reduce the bioavailability (Def. 5 at p. 4) of the intact drospirenone (PTX 104).

A. *Micronization and Formulation of Enteric Coating*

For Tack, isomerization of drospirenone in vitro presented a significant roadblock. As a result, on September 20, 1983, Dr. Tack recommended an enteric coated (Def. 10 at p. 5) formulation and requested a delay in the development schedules so that an enteric coated tablet could be developed (PTX 007).

On November 29, 1983, Dr. Tack reported on the results of his September, 1983 in vitro study of drospirenone in hydrochloric acid (PTX 104) where he found that drospirenone isomerized in acid. At that time, Dr. Tack wrote:

> [Drospirenone] is transformed rapidly and to a considerable degree into its inactive isomer, ZK 35 096, in hydrochloric acide medium at 37 degrees C. If the results obtained in vitro are applied to in vivo conditions, it can be presumed that, with an assumed gastric juice volume of 100 ml, the majority of the dose (solubility of drospirenone 5-10 mg/1) passes into solution during passage through the stomach and consequently undergoes rapid isomerization. A clear reduction in the bioavailability of the unchanged active substance is to be expected as a result.
>
> The planned studies on the progestogenic efficacy of [drospirenone] should therefore be performed with an enteric coated formulation.

(PTX 104).

In late 1983, Dr. Tack considered whether there were any alternative dose forms to enteric coating. In order to do so, he made some handwritten theoretical calculations on a single sheet of paper using a "compartment model" (PTX 206). The compartment model appears to be a mathematical method which weighs certain variables (rate of dissolution, rate of isomerization and gastric emptying time); and then extrapolates a range of the best and worst case scenarios for attaining bioavailability of drospirenone. The purpose of the modeling was to illustrate (a) the transformation kinetics of drospirenone, and (b) to ascertain whether there was an alternative to enteric coating under different conditions including micronization. Tack theorized that "formulations with macro product or sustained-release forms might be alternatives to enteric coating." (PTX 206). According to his calculations, Tack concluded that increasing the dissolution rate of drospirenone through micronization may lead to increased isomerization (PTX 206).

As a result, from 1983 to the beginning of 1988, based upon Dr. Tack's in vitro experiments and compartment model math, Bayer used an enteric coated formulation in a series of studies involving beagles and humans in order to test for an increase in the bioavailability of drospirenone. The studies are briefly summarized.

* In a study conducted from September 1984 through March 1985 with five human female subjects, the results showed significant intra-and inter-individual differences regarding bioavailability after administration of an enteric coated formulation containing micronized drospirenone (PTX 17 at 3; 6T 13, 21 through 14, 16).

* In a study dated November 19, 1984, three beagles were intravenously given drospirenone, and three weeks later were orally administered drospirenone in an enteric coated tablet. The study found "marked interindividual difference" with the enteric coated tablet (PTX 106).

* In a July 17, 1985 study, an enteric coated table [sic] was administered to five human females at various dose amounts. The test concluded that there was a lag time for absorption to occur, and there were intra- and inter-individual variances (PTX 17).

* In a July 25, 1986 study of five women, two received a 1 mg dose of drospirenone, and three received a 2 mg dose. It was concluded that the 1 mg dose did not inhibit ovulation, while the 2 mg dose suppressed ovulation (PTX 198).

* In another study dated July 25, 1986, a 2 mg dose of drospirenone was administered to eight females. The result was that, in five of the eight subjects, "inhibition of ovulation with the 2 mg dose . . . was borderline." (PTX 198).

* In a study dated September 9, 1987, six beagles were given a normal tablet, and then an enteric coated tablet of drospirenone. The conclusion stated "the present results in the dog indicate that the aggregate bioavailability can be achieved with tablets without a coating resistant to gastric juices." (DX 451).

In 1985, another Bayer scientist, W. Losert, published an article on the effects of drospirenone on rats. Although the rats received injections of the drug, the author concluded that "drospirenone exhibited progestogen and antimineralocorticoid activity in the same dose range. It will most probably

exert both effects after oral administration in humans (Def. 3 at p. 4)."[7]

In 1986, Nickisch, a Bayer scientist, published an article about the isomerization rate of drospirenone in vitro (JX 003). Although Losert, Nickisch, and Tack all attended the 1983 strategic meeting (see p. 12-13) and performed similar studies, there is no evidence that the three had collaborated on the experiments.

B. *Change to Non-Enteric Coated Formulation*

On February 17, 1988, Dr. Tack presented a lecture on the use of the "compartment model" to doctoral candidates in pharmacy at the Free University as a means to determine whether certain "carbolactones" needed an enteric coating (5T 127, 14-25). Despite his lecture, and at about the same time as his University presentation, Tack and Dr. Hümpel, a colleague, brainstormed about characterizing the extent of isomerization of unprotected drospirenone in vivo (5T 130, 4-20). It is unexplained why Tack changed course on this subject after four years. Tack called this study the "third arm" of a broader study. This third arm measured the loss of bioavailability attributable to isomerization of drospirenone tablets in stomach acid (5T 132, 22-25). Dr. Tack testified that the non-coated tablets were immediate release tablets. The result was that drospirenone did not isomerize. In a study dated July 7, 1988, Bayer conducted in vivo tests of eight women comparing the bioavailability results between enteric coated and immediate release tablets. The conclusion stated "for future studies, the normal tablet should be used

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[7] W. Losert, *Progestogens with Antimineralocorticoid Activity* (1985) (PTX 0100).

because in comparison with the enteric coated tablet, ZK 30b95 was absorbed (Def. 1 at p. 4) more rapidly with less inter-subject variability from the normal tablet." (PTX 12).

To Tack's surprise, the non-enteric coated drospirenone tablets had the same bioavailability as the enteric coated tablet (5T 136, 20 through 137, 15). According to Tack, subsequent to this finding, Bayer changed the development path of drospirenone and pursued the non-enteric coated formulation because "there was no further reason to stay with the enteric-coated formulation." (5T 137, 16-20). After this finding, Bayer commenced the process of developing an oral contraceptive containing drospirenone without enteric coating.

2. *Clinical Trials and Previous Patents*

Between 1989 and 1997, Bayer conducted at least five clinical trials to determine the efficacy and effectiveness of the combination of drospirenone and ethinylestradiol (see generally Heithecker Dep. Designations). Below are the most important of the trials conducted.

Simultaneously, from January 1990 to September 1990, Bayer conducted a Phase II dosage trial in Europe. In this trial, 52 volunteers aged 20-35 were administered a combination of either 3 or 2 mg of drospirenone in combination with ethinylestradiol over a period of time. On May 15, 1992, Bayer scientists tentatively concluded that the 3 mg tablet was found to be the best option because its ovulation inhibiting effect was demonstratable in all cases (DX 4).

On August 16, 1995, Bayer produced a Masterplan entitled "OC with drospirenone." The Masterplan established a timeline for bringing the product to

market including such factors as development, production, marketing, and government approvals.[8]

From December 1992 through April 1996, Bayer conducted a Phase III clinical trial in Europe on the drospirenone/ethinylestradiol combination. The purpose of the study was to "obtain data on the contraceptive reliability, cycle control, and tolerance (including blood pressure, heart rate, and body weight) of the test product in long-term contraceptive use (up to 26 cycles) in comparison to the desogestrel-containing preparation Marvelon.®" The formulation was 30 μg ethinylestradiol plus 3 mg drospirenone for oral contraceptive over 21 days, followed by a 7-day tablet-free interval (DX 2 at p. 2). About 900 females participated. About half of the group was administered the test product (the Yasmin® Formulation) and the other half was administered Marvelon®, a well-known oral contraceptive commercially available in Europe, manufactured by a competitor of Bayer.

In 1996, Jürgen Spona obtained a patent entitled "Pharmaceutical Combination Preparation For Hormonal Contraception," bearing U.S. Patent No. 5,583,129 ("the Spona Patent"; DX 00456). It teaches to formulate an oral contraceptive containing estrogen (17 β-estradiol and ethinylestradiol) combined with a gestagen including, but not limited to drospirenone (.1 to .3 mg) in tablet form for 23 or 24 days followed by 5 or 4 placebos for a total of 28 days. The Spona Patent is a pill-taking regimen. This patent does not explicitly teach the formulator to expose micronized drospirenone to stomach acid. Rather, it generally advises that "[t]he formulation of an estrogen and

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[8] The parties, by agreement, redacted portions of the Masterplan concerning patent applications (DX 277).

gestagen for the use according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredient." (DX 456 at col. 5, 26-27) The purpose of the invention is to ameliorate side effects from estrogen.

In 1998, Gast filed for a patent entitled "Monophasic Contraceptive Method and Kit Comprising a Combination of a Progestin and Estrogen" for a new oral contraceptive drug regimen. Although the applicant does not mention micronization or immediate release formulation, the "preferred daily dosage" is a combination of drospirenone/ethinylestradiol "admixed together" in a single dose utilizing "conventional methodology." (DX 55). The purpose of the invention is to provide effective contraception "with minimal side effects while greatly reducing total contraceptive steroid administered." (DX 55). As in the Spona Patent, this is an application by a non-Bayer employee prior to public marketing.

On April 20, 1998, after tabulation and verification of the results of the Phase III clinical trial in Europe, Bayer concluded "[b]oth study preparations were found to be effective with regard to contraceptive reliability and cycle control." There was some weight gain in subjects who took Marvelon®, and a weight reduction with the drospirenone/ethinylestradiol combination (DX 2).

On May 26, 1998, Lachnit, an employee of Bayer who attended the 1983 meeting about the development of drospirenone, obtained a patent entitled "Pharmaceutical Combination Preparation for Hormonal Contraception" bearing U.S. Patent No. 5,756,490 ("'490 Patent") (DX 457). The patent is a pill-taking regimen aimed at reducing the overall

intake of estrogen. The patent calls for a regimen of active ingredient pills for 23 or 24 days plus an additional estrogenic component of 4-8 days depending on the length of the woman's menstrual cycle. One of the "preferred embodiments of the invention" is a combination of ethinylestradiol and drospirenone formulating same "completely analogously to the way already known for conventional oral contraceptives." (DX 457).

At some point, Bayer determined it would market drospirenone/ethinylestradiol under the name Yasmin® in the United States. Accordingly, the FDA would be required to approve such distribution. Internally, there was some debate whether Bayer could solely rely on the European studies as its foundation for FDA approval. Bayer determined that the subjects in the clinical trial in Europe were overwhelmingly Caucasian, and due to the more diverse population of the United States, a clinical study in the United States was warranted (9T 33, 19 through 34, 21).

From December 9, 1996 through July 16, 1998, a Phase III clinical study was conducted in the United States (PTX 163). The U.S. Phase III clinical trial enrolled 333 women from six geographically distinct study sites. As noted above, it differed from the European Phase III study because the subjects were from more diverse backgrounds. The subjects were given Yasmin®. The results confirmed those of the European studies—Yasmin® effectively inhibited ovulation and had aldosterone antagonist and anti-androgenic (Def. 4 at p. 4) qualities.

Participation in the U.S. clinical trial was fashioned in a manner to meet certain criteria including race, age, smoking habits, and medical history (JX 10). During the trial, participants consented to monitoring

by a doctor, and agrees [sic] to maintain a daily log. Participants executed an informed consent form, but did not sign a confidentiality agreement about the claimed patent. Unlike the participants, the external organizations who supervised the U.S. clinical trial were subject to rigid protocols. The employees of the external groups are called principal investigators. The principal investigators were provided with an "Investigator's Brochure" which "summarizes everything that the company knows about a drug or a drug product" at that time (8T 30, 8-13). The investigator's brochure is conspicuously marked as "confidential." It states in part:

> Information contained herein is for the use of investigators only and may not be reproduced in writing or in oral presentation without the permission of [Bayer].

Bayer required the investigators to obtain its prior approval of any publication about the claimed patent to a third party in order to "prevent premature disclosure of trade secrets or otherwise patent-protected materials." (JX 19; Ellman Decl. Ex. C; investigator agreement letters at SBPL 03500855). According to Dr. Shulman, principal investigators are subject to confidentiality provisions. Principal investigators (a) may not divulge the data collected; (b) must use the product according to protocol; (c) may not prescribe the test product to non-participants, and (d) must secure the test product in a safe location (9T 27, 14-23; JX 10).

During the U.S. trial the study subjects and the clinical investigators were informed of the active ingredients of the claimed patent. This disclosure was necessary—obviously, for example, a participant taking a regimen of drugs requires the liberty of

discussing same with a spouse, medical personnel in case of emergency, etc. (8T 29, 16-20). In addition, some study subjects did not return all the unused study drug. Dr. Ellman noted that it is "very common" for some of the unused test product not to be returned in a clinical trial of this size and duration (8T 31, 15-20). In order to minimize any breach of security, Bayer monitored the U.S. clinical trial by frequent and repeated visits to the study sites (8T 12, 11-21) and by extensive record keeping (JX 10). As part of the application, the results of the Phase III U.S. clinical trial and the Phase III European clinical trial were submitted to the FDA in order to establish the contraceptive effectiveness of Yasmin® (8T 9, 23 through 10, 4).

Shortly after the completion of the U.S. clinical trial and tabulation of its results, on January 7, 2005, Bayer filed its New Drug Application ("NDA") with the FDA which was "voluminous, comprehensive and detailed." (JX 34; 8T 19 through 20, 17). Thereafter, the FDA ultimately approved Bayer's NDA, and Bayer commenced marketing Yasmin® in the United States sometime in June, 1999 (8T 20, 19-22).

3. *The '531 Patent Prosecution*

On August 31, 1999, Bayer filed a provisional application for a patent for the oral contraceptive, and exactly one year later, the final application for the '531 Patent was filed (JX 6; 1T 16, 8-14). The patent process proved to be a bumpy road. Prior to its approval, the patent examiner rejected the claimed invention on at least three occasions for various reasons including obviousness: September 13, 2001; June 4, 2003; and March 23, 2004 (JX 2 at p. 0325, 0693 and 1586).

On September 13, 2001, the examiner rejected the application due to obviousness. More specifically, the examiner found that many of the claims were not patentable over the Gast patent (see, p. 19). The examiner found that it would have been obvious to a person of ordinary skill in the art to employ drospirenone and ethinylestradiol in micronized form as a means to increase bioavailability because Gast disclosed a similar dosage range and regimen.

In response to the September 13, 2001 rejection, Bayer submitted a declaration by Dr. Ralph Lipp, an inventor of the '531 Patent (JX 2 at p. 618-21). In his declaration, Lipp relied on the Nickisch article (JX 3) to show that drospirenone was acid sensitive and, when exposed to hydrochloric acid in a beaker, converts to 8 parts isomer to 2 parts drospirenone. In addition, Lipp referred to a number of articles which allege that the prior art indicates "micronization of other drugs does not necessarily lead to increased bioavailability over other forms or can be detrimental to bioavailability." (JX 11 at p. 0620).

On June 14, 2003, in response to Lipp, the examiner stated that Gast and Elliesen taught the combination of drospirenone and ethinylestradiol in a 28 dosage kit with 3-5 placebo doses. The examiner found that "[o]ne of ordinary skill in the art would have been motivated to employ micronized drospirenone dissolved by any method because micronized drospirenone is known to be useful in combination compositions as taught by Elliesen." (JX 2). More particularly, the examiner was not persuaded by the Lipp declaration. The examiner specifically rejected Dr. Lipp's contention that the isomerization of drospirenone at low pH stomach levels would direct a

skilled person not to orally administer micronized drospirenone (JX 2 at 693).

On December 12, 2003, Bayer submitted the declaration of Dr. Herman Ellman concerning prior public use and the U.S. Phase III clinical trial. Dr. Ellman's declaration explained the details of the U.S. clinical trial of Yasmin® which occurred prior to the filing of the '531 Patent (JX 10).

Barr argues that a reasonable examiner would have considered the omitted information concerning the European trials material to the patentability of the invention (5T 6, 19 through 7, 3).

Barr alleges that Bayer and Dr. Heithecker had concluded that the drug was a reliable and safe contraceptive according to results shown in Research Report 9693, the Masterplan, and the AI 51 Report. These results are allegedly contrary to the statement in Dr. Ellman's declaration that Bayer lacked the information need to determine whether the clinical study drug was safe and effective for its intended purpose (DX 277; 4T 107, 16 through 108, 25). Accordingly, since there had been an actual reduction to practice of the invention during the European clinical trials, Barr alleges the U.S. clinical trial could not be experimental. Therefore, the U.S. clinical trial constituted a public use of the invention prior to the critical date (4T 90, 25 through 92, 3). According to Barr, Dr. Ellman's statement that the U.S. clinical trial was experimental was therefore false and misleading (2T 67, 7-9).

In paragraph 31 of his declaration, Dr. Ellman stated that "[n]ot only was the Clinical Study confidential, controlled and closely monitored by Bayer, but it was also experimental in nature." (JX 10). Dr.

Ellman testified that the purpose of his declaration was to give the Patent Office information about a potential § 102(b) public use—the U.S. clinical trial—and not any of Bayer's European clinical trials (8T 39, 1-4). Dr. Ellman believed in 2003, and continues to believe today, that the U.S. trial was confidential and experimental (8T 22, 18-23).

On March 23, 2004, the application was rejected yet again. According to the patent examiner, this rejection was based on a prior art reference identified as De Castro '270) [sic] (JX 2 at SBPL03501586.). The patent examiner noted that the De Castro '270 patent "[taught] a method of preparing very small drug particles, less than 400 nm, for poorly soluble drugs such as steroids in order to increase the bioavailability of the drug." (JX 2). The patent examiner found that "[p]ossessing the teaching of De Castro, one of ordinary skill in the art would have optimized the particle size of the herein claimed compounds to increase the bioavailability of the same." (JX 2).

On March 29, 2004, in response to the rejection based on De Castro, Bayer filed a reply, arguing in part:

> [B]ased on the known properties of drospirenone one of ordinary skill in the art would not have been motivated to micronize or provide it in a form promoting its rapid dissolution. In fact, one would have been directed away from providing it in a form promoting rapid dissolution in view of its known isomerization to an inactive form under acidic conditions (such as in the stomach upon oral administration).

(JX 2 at SBPL03501665).

At that time, Bayer also submitted a request for correction of inventorship (JX 2). The original application had not included inventors Tack and Hümpel. According to Bayer:

> In the mid to later 90s, the originally named four inventors [Heil, Heithecker, Hilman, and Lipp] independently took up this earlier development [by Tack and Hümpel] and, as a result, these four caused the above-identified patent application to be drafted. As filed, it included claims to the inventions of both the earlier 2-man inventive entity (including kits for the 21/7 day regimen) and the 6-man inventive entity (kits for oral contraception regimens different from the 21/7 day regimen).

(JX 2 at 1690).

On May 19, 2004, Bayer further amended the '531 Patent claims to include the claim "*exposed to the gastric environment upon dissolution,*" and submitted the declaration of Dr. Adrian Funke in support thereof (JX 2) (emphasis added). In an attempt to address the patent examiner's concern with the De Castro '270 Patent, the declaration states in part: "[T]he examiner seems to argue that DeCastro [sic] teaches micronization straightforwardly leads to increased bioavailability for steroid drugs by particle size reduction. However, this clearly cannot be applicable to drospirenone . . . . Nickisch teaches that an increased exposure to the environment of the stomach, which would occur upon an increase in the rate of dissolution of drospirenone, will lead to an enhancement of the deleterious isomerization of drospirenone." (JX 2).

On July 2, 2004, the patent examiner allowed the claims. The patent examiner's "reasons for allow-

ance" cited the Funke declaration filed on May 19, 2004 (JX 2), and the declarations filed December 9, 2003[9] (JX 2 at 1722 and 1665).

The patent examiner states that he relied on these declarations for the proposition that drospirenone was unstable in acidic environments and micronizing synthetic progesterone was unobvious. The patent examiner also cited Bayer's Reply to the March 23, 2004 Rejection as a basis for allowance. Specifically, the patent examiner found the reply as persuasive in overcoming the 35 U.S.C. § 103(a) obviousness rejection. Relying on Lipp, the examiner found that "[t]he micronized drospirenone will be degraded even more rapidly because micronization exposed the drug particles to the acidic environment of the stomach; an oral dosage form "containing the drospirenone particles, which exposed to the gastric environment upon dissolution, would be unobvious [sic] in view of the data presented in the declaration filed December 9, 2003." (JX 11, Lipp Decl. Appendix A; JX 2 at SBPL03501722).

On September 7, 2004, the '531 Patent entitled "Pharmaceutical Composition for Use as a Contraceptive," was issued to the predecessors of Bayer. The product subject to the '531 Patent is now known commercially as Yasmin®.

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[9] While this issue does not affect the outcome this Court notes that it is unclear which specific declarations the patent examiner is referencing, when referring to the December 9, 2003 declarations. The Ellman Declaration was filed on December 12, 2003. It is unclear from the patent prosecution history what other declaration was filed on December 9, 2003. The Lipp Declaration was filed on March 10, 2003, a much later date.

The '531 Patent is an oral contraceptive described as an oral dose form containing 2-4 mg micronized drospirenone and 0.01-0.05 mg 17 α-ethinylestradiol for use as a contraceptive in a human female (see generally JX 1). Bayer sells Yasmin® tablets in the United States in a 28-day oral regimen that consists of 21 tablets containing 3 mg drospirenone and 0.03 mg 17 α-ethinylestradiol each, plus 7 placebos. *Id.*

On January 5, 2005, Barr submitted to the FDA an ANDA for Product No. 77-527, a generic version of Yasmin®, to the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of same.

On March 18, 2005, Barr sent notice to Plaintiffs that the FDA received Barr's ANDA. Bayer filed the instant action on April 29, 2005.

V.

ASSESSMENT OF THE INVENTION DEVELOPMENT PATH EVIDENCE

By way of background, Bayer asked this Court to review testimony and documents concerning the internal development path of drospirenone. Barr strongly objected to these inclusions, arguing this information was not part of the prior art, and thus not pertinent to the obviousness inquiry, a fact that Bayer conceded. However, as discussed below, this Court allowed testimony and documents as potentially probative information, according it the appropriate evidentiary weight. The parties agree that the internal studies regarding drospirenone do not constitute prior art (5T 147, 3-11). Accordingly, prior to trial, Barr moved to strike the internal studies, and to bar Tack's testimony as irrelevant. The Court overruled the objection on the basis that the evidence

may be "probative of how the person of ordinary skill in the art would read the published results." (Barr's Proposed Findings of Fact at ¶ 177); *see Sanofi-Synthe Labs v. Apotex, Inc.*, 470 F.3d 1368 (Fed.Cir.2006). Accordingly, the Court considered the claimed "invention's development path" in determining obviousness. The *Sanofi* case is instructive in this regard. In *Sanofi*, the evidence was that Sanofi had spent "four years and millions of dollars" prior to redirecting its efforts on the right course to develop a substance known as clopidogrel bisulfate. *Id.* at 1378-79. According to the trial court in *Sanofi*, plaintiff had "extensively test[ed] the racemate PCR 4099 before deciding to try separating the enantiomers of the racemic mixture." This second path of development proved to be innovative and successful. *Sanofi-Synthe Labs v. Apotex Inc.*, 492 F.Supp.2d 353, 390-91 (S.D.N.Y. 2007). Although consideration of an invention's development path is probative of an obviousness defense, the issue remains how much weight the Court should accord such evidence.

The Court sits as the trier of fact and law. As such, the Court assesses the credibility of witnesses and deduces facts from direct and circumstantial evidence. Like a jury, the Court determines the trustworthiness of testimony by assessing the demeanor of the witnesses and whether their statements were honest and forthright. In this case, Dr. Tack testified extensively about the earlier development path of drospirenone. His testimony was evaluated by employing the same factors as a jury is instructed to use. Third Circuit Model Jury Charges § 1.7; *Utilities, Inc. v. Blue Mountain Lake Assoc.*, 121 Fed. Appx. 947, 949 (3d Cir.2005). For the reasons stated below, the Court finds the testimony of Dr. Tack and

other internal development path evidence to be of little probative value.

First, the person of ordinary skill in the art must consider all the prior art available as of the date of filing for the patent (August 31, 1998). Dr. Tack performed his work between 1983 and 1988. There is at least a ten-year hiatus between Tack's assessment of the issue and the time of the person of ordinary skill in the art's assessment. From ordinary experience, one can reasonably conclude that there were significant advances in pharmaceutical formulation during that time period just as there were advances in other aspects of life generally (i.e. the development of the internet). Facts that were not obvious in the 1983-88 time frame may have been in 1998. Recognizing the common sense of this notion, the Court is leery of equating Tack's testimony about internal development, as well as his perception of the prior art, to that of a person of ordinary skill in the art on August 31, 1999.

Second, Dr. Tack relied on a "compartment model" to confirm his assessment that drospirenone required an enteric coating (PTX 206). The compartment model appears to be a mathematical method to weigh certain variables (rate of dissolution, rate of isomerization, gastric emptying time) and then, by extrapolation, determine a range of best and worst case outcomes regarding the bioavailability of drospirenone (5T 113-122). Tack's handwritten compartment model conclusions were completed in 1983. Dr. Tack did not provide any citation to the prior art which confirms the trustworthiness of the model—that is, whether it was a generally accepted compartment model used in the field of pharmacology. He attempted to cloak the model with academic credentials by lecturing on

the compartment model in 1988 to some doctoral students at a university. The Court is not impressed. In absence of any substantial support in the prior art, it is difficult to conclude that a person of ordinary skill in the art would have employed such a model in the decision making process.

Third, some of Dr. Tack's testimony lacks credibility. As noted above, Dr. Tack testified that his lecture on the compartment model to the doctoral students occurred in early 1988. In that same month, despite his obvious commitment to the compartment model, he suddenly abandoned the compartment model results, reversed grounds, and agreed that an absolute bioavailability test of drospirenone should be conducted. In effect, Dr. Tack discarded the compartment model without adequate explanation, except to say that he had a conversation with a colleague, Dr. Hümpel (5T 132, 9 through 133, 12). This abrupt turnaround does not make sense.

Fourth, Dr. Tack was also inconsistent on at least one point. Notably, Dr. Tack testified that immediately following the finding that drospirenone did not require an enteric coating (5T 136, 21), Bayer abandoned the use of such coatings (5T 137, 18-20). However, later in his testimony, Tack identified an internal Bayer report (PTX 85) which states that Dr. Oelkers used enterically coated drospirenone tablets several years later in an experiment. The inconsistency in his testimony raises doubts about Tack's recollection of events.

Fifth, Bayer argues that Tack qualifies as a person of ordinary skill in the art as defined herein since Tack received his doctorate in 1978 (Def. 18 at p. 7). The Court is less than certain. Since Tack worked in a marketing department for 2-3 years immediately

after his graduation (5T 49, 4-13) as opposed to a laboratory, it is fair to conclude that his skills as a formulator probably regressed or slipped during that time period. Upon his transfer to the Galenics Department, some honing or refreshing of his skills was most likely necessary. His first major assignment in the Galenics Department was the formulation of drospirenone (5T 52, 8-10). During this initial time period in the Galenics Department, the Court is not convinced that Tack possessed the qualifications of a person of ordinary skill in the art as defined herein.

Sixth, the internal invention path evidence proffered is incomplete, and leaves more questions open than resolved. According to Bayer, at the 1983 strategic meeting, Tack was the only person assigned to developing drospirenone. If so, why did other attendees at the meeting continue to perform research? For instance, (a) in 1985 attendee Dr. Losert published an article on his work with rats and progestins with antimineralocorticoid activity, including drospirenone; (b) in 1986 attendee Dr. Nickisch published an article on the isomerization rate of drospirenone in vitro; and (c) in 1997, attendee Dr. Lachnit obtained a U.S. Patent for an oral contraceptive regimen which included drospirenone and ethinylestradiol. The evidence suggests that the internal invention path was unorganized and undisciplined. As such, a lack of credibility clouds Bayer's explanation of events.[10]

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[10] The declaration submitted to PTO regarding an amendment to inventorship on March 24, 2004 is also wrong. In that declaration, Bayer stated that "in the mid to late 90s, the originally named four inventors [Heil, Heithecker, Hilman and Lipp] independently took up "[sic] the research of Tack and

Seventh, at trial, Bayer through Tack's testimony, introduced many of the internal reports; Tack was not the author of such reports, and he lacked personal knowledge of their contents. To that extent, the probative value of these internal reports is questionable.

Accordingly, the Court gives little weight to Tack's testimony and internal development path evidence generally, as being probative of how a person of ordinary skill in the art would review the published art as of the critical date.

VI.

OBVIOUSNESS

1. *Burden of Proof and Standard of Review*

Barr has the burden to prove obviousness by clear and convincing evidence. The '531 Patent is presumed valid. 35 U.S.C. § 282. "The presumption of validity is based on the presumption of administrative correctness of actions of the agency charged with examination of patentability." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1569 (Fed.Cir.1996). Barr's affirmative defense of obviousness is based on 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

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Hümpel. It is quite clear from the record that Heithecker commenced clinical trials as early as 1989. Although this misstatement is not germane to the outcome, it illustrates a general lack of candor regarding the internal development process.

> subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Barr has "[t]he burden of establishing invalidity of a patent or any claim thereof." 35 U.S.C. § 282. Barr must prove each fact underlying the Court's determination of obviousness by clear and convincing evidence. *See Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1558 (Fed.Cir.1986). The U.S. Supreme Court has defined "clear and convincing evidence" as evidence that places in the Court, as factfinder, an "abiding conviction that the truth of its factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984) (internal quotation marks omitted). The burden of persuasion remains with Barr and does not shift to Bayer, the patent holder. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed.Cir.1983); *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed.Cir.1984).

Decades ago, the Supreme Court elucidated how obviousness is to be determined. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). The Court stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be

> utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquiries may have relevancy.

Id.

About a year ago, the Supreme Court reaffirmed the *Graham* test and rejected the strict application of formalistic obviousness tests which crept into our jurisprudence over the last forty years. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). In *KSR*, Teleflex sued KSR for infringing upon a patent entitled "adjustable pedal assembly with electronic throttle control" (the "Engelgau Patent"). In broad terms, the Engelgau Patent combines an electronic sensor with an adjustable automobile pedal so that a signal is transmitted to a computer that controls the throttle, so the operator may regulate the speed of the vehicle. By way of background, before computers, the accelerator pedal operated via a cable that controlled the throttle which opened and closed valves in order to control speed. In the 1990s, the cables were replaced with electronic sensors that transmitted a signal to a computer-controlled throttle. At the same time, the position of the gas pedal became an issue for "drivers of smaller stature." *KSR*, 127 S.Ct. at 1735. To remedy this issue, inventors designed an adjustable pedal with integrated sensors. There were several existing patents dealing with various issues regarding adjustable pedals. The Asano Patent adjusts the pedal position but the pivot point (where signal transmission initiates) stays fixed. The Redding Patent utilizes a sliding model where both the pivot point and the pedal adjust. Simultaneously, other

inventors were developing modular sensors, i.e. sensors "taken off the shelf" and attached to the pedal. *KSR*, 127 S.Ct. at 1729. It appears that all the patented solutions were less than perfect, particularly the Redding device, where certain wires had a tendency to fray.

In 1998, Ford hired KSR to supply an adjustable mechanical pedal system for which it obtained a patent ("'976 Patent"). In 2000, General Motors ("GM") contracted with KSR to supply an adjustable pedal for computer-controlled throttles. To make the '976 Patent mechanical pedal work on the computer-controlled throttle GM required, KSR attach [sic] a modular "off the shelf" sensor at the pivot point.

Teleflex, the assignee of the Engelgau Patent, believed this infringed upon its patent. The Engelgau Patent claims that it is a "position-adjustable pedal assembly with an electronic pedal position sensor attached to the support system of the pedal assembly. Attaching the sensor to the support member allows the sensor to remain in a fixed position while the driver adjusts the pedal." *Id.* at 1737.

Teleflex sued, claiming the KSR/GM solution infringed upon its Engelgau Patent. KSR countered that Engelgau Patent was obvious based upon the Asano Patent. The Asano Patent was not disclosed within the prior art references or in the patent prosecution by Engelgau. *Id.* The trial court, utilizing the *Graham* test, found "little differences" between the Asano and Engelgau Patents, except for the use of a sensor which was covered by other patents. *Id.* at 1738. Hence, the District Court concluded that the Engelgau Patent was obvious. *Id.*

In the interim years, between the *Graham* decision and the present day, the Federal Circuit adopted the so-called teaching, suggestion, or motivation test ("TSM test") to determine obviousness. Under the TSM test, a patent claim is obvious only if some "motivation or suggestion to combine the prior art teachings can be found in the prior art, the nature of the problem or the knowledge of a person having ordinary skill in the art." *Id.* at 1734 (internal quotation marks omitted). Applying the TSM test, the Circuit Court in *KSR* reversed the District Court's decision.

The Circuit Court reasoned that "unless the prior art references addressed the precise problem that the patent was trying to solve, the problem would not motivate an inventor to look at those references." *Id.* at 1738 (internal quotation marks omitted). The Circuit Court conceded that it may have been obvious to try the combination of the Asano Patent with an off-the-shelf sensor, but this was irrelevant because according to the Circuit Court, "obvious to try has long been held not to constitute obviousness.["] *Id.* at 1739 (internal quotation marks omitted).

The Supreme Court granted certiorari because "the Court of Appeals addressed the question of obviousness in a manner contrary to § 103 and [its] precedents." *Id.* at 1735.

Justice Kennedy, in writing for a unanimous Court, rejected the Circuit Court's "rigid approach." *Id.* at 1739. The Court reaffirmed *Graham*'s "functional approach," which "set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive." *Id.* According to Justice Kennedy, the Circuit Court erred for several reasons. First, the Circuit Court had

adhered to a "formalistic conception of the words teaching, suggestion and motivation or by overemphasis on the importance of published articles and the explicit content of the issued patents." *Id.* at 1741. The Court reasoned that "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id.*

Second, the Circuit Court's application of the TSM test too narrowly assumes that a person of ordinary skill in the art would only consider references in the prior art which are designed to solve the same problem. *Id.* at 1472. Justice Kennedy found that "[c]ommon sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.*

Third, the Supreme Court faulted the Circuit Court's rejection of the theory that a claim will not be obvious based on a "combination of elements [that are] 'obvious to try.'" *Id.* The Supreme Court reasoned that where there is a "finite number of identified, predictable solutions, a person of ordinary skill [in the art] has good reason to pursue [them]." *Id.* This "is likely the product not of innovation but of ordinary skill and common sense." *Id.* The principles of *KSR* have been applied in pharmaceutical cases. *See, e.g., Takeda Chemical Indus. v. Alphapharm*, 492 F.3d 1350 (Fed.Cir.2007), *pet. for cert. filed* 75 USLW 3374 (Dec. 20, 2007) (No. 07-838).

Fourth, the Supreme Court found that the Circuit Court erred by applying "[r]igid preventative rules

that deny factfinders recourse to common sense." The Supreme Court noted that such rigid rules "are neither necessary under our case law nor consistent with it." *KSR*, 127 S.Ct. at 1742-43.

With this legal backdrop, the Court evaluates the obviousness of the '531 Patent, as enunciated in *Graham* and *KSR*.

In this case, the Court is asked whether it was obvious to a person of ordinary skill in the art as of the August 31, 1999 [sic] to (1) micronize drospirenone so as to increase its bioavailability, and (2) not protect the drospirenone from the gastric environment with an enteric coating (7T 62, 15 through 67, 4; JX 1 at cols. 10-16).

The parties agree that the following limitations were well known in the art at the time the '531 Patent application was filed: (1) 2-4 mg drospirenone; (2) in combination with 0.01 to 0.05 mg 17 α-ethinylestradiol; (3) along with pharmaceutically acceptable carriers; (4) in a kit which contains 21 tablets with active ingredients and 7 placebos; (5) used as an effective oral contraceptive in human females (7T 149, 1-5; JX 001).[11]

Bayer claimed at trial that the nonobvious innovation of the '531 Patent was that 2-4 mg drospirenone could be micronized to increase its bioavailability, and that the micronized drospirenone need not be protected from the gastric environment by means of enteric coating (6T 53, 5-6; JX 1, at col. 3, ll. 4-13).

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[11] As the parties agree, these same limitations are also referred to within the kit claims (8, 29, 36, and 50), so the Court does not distinguish them in its analysis (Docket Entry No. 172, ¶ 17).

As a consequence, the obviousness inquiry focuses on the formulation of, and dose form of, the oral contraceptive combination of drospirenone and ethinylestradiol. The two characteristics of drospirenone that dominate the obviousness inquiry are its poor water solubility (Def. 19 at p. 7) and acid sensitivity. As a result of these characteristics, Bayer alleges drospirenone presents special issues to the formulator, such as whether to micronize or enteric coat the product. These issues must be addressed when developing the appropriate formulation and dose form, and therefore are reviewed during the obviousness inquiry.

More specifically, the Court evaluates obviousness following the *Graham* test as elaborated on in *KSR*. The factors are: (1) "the scope and content of the prior art"; (2) the "differences between the prior art and the claims"; (3) "the level of ordinary skill in the pertinent art"; and (4) "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." *KSR*, 127 S.Ct. at 1734.

"[P]rior art relevant to nonobviousness includes the following: 1. printed publications or patents from anywhere in the world that were published or issued before the applicant's date of invention; 2. prior use or prior knowledge that occurred in the United States before the applicant's date of invention; 3. a U.S. patent application by a different inventive entity that subsequently issued and was filed before the applicant's date of invention; and 4. another's invention that was made in the United States and that was not abandoned, suppressed, or concealed before the invention date of the invention in question." Herbert F. Schwartz, Patent Law and Practice § 4.I.D.2.a, p. 86 (5th ed.2006).

"Of course, the correct test of invention or nonobviousness focuses on the teachings of the prior art as a whole, not the disclosures of individual references taken singly." 2-5 Chisum on Patents § 5.04, n. 14. "When the references are all in the same or analogous fields, knowledge thereof by the hypothetical person of ordinary skill is presumed, . . . and the test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed.Cir.1991) (quoted in 2-5 Chisum on Patents § 5.04).

2. *The Level of Ordinary Skill in the Art Under* Graham

Under the *Graham* test, the Court must resolve, among other things, the "level of ordinary skill in the pertinent art." 383 U.S. at 17. The parties mostly agreed about the level of skill required.

Both parties submit that a person with a doctorate in a field related to pharmaceutical formulation meets the skill level. In addition, Barr asserts that a person with an undergraduate degree in a similar field plus ten years of experience qualifies (1T 30, 14-22). Bayer believes an undergraduate need only possess several years of experience in formulation (6T 60, 14-22). The Court finds the latter is appropriate. For clarity purposes, the definition (Def. 18 at p. 7) is as follows:

> Person of ordinary skill in the art is a hypothetical person, who at the time of the invention, has either (1) a Ph.D. in a field related to pharmaceutical formulation and processing (such as physical chemistry, medicinal chemistry, or pharmaceutics) or (2) a similar undergraduate

degree and at least several years of experience in formulation (1T 30, 14-22 and 6T 60, 14-22).

3. *The Scope and Content of the Prior Art under Graham*

As directed by the '531 Patent claims at issue, there are three general areas of prior art for this Court to review. The Court will proceed to review these general areas of prior art (in vitro/in vivo correlation, micronization, enteric coating), and then address the more specific references such as Krause, Nickisch, and the other prior art.

A. *In Vitro/In Vivo Correlation (Def. 11, 12 at p. 6)*

The prior art is clear that in vitro testing can not be the sole basis upon which a drug dose form decision is made. The prior art, as set forth in a pharmacologist hornbook by Robert Aulton,[12] is squarely on point. Both parties' experts opine as to what Aulton teaches with respect to in vitro and in vivo studies (Bayer's Proposed Findings of Fact; Barr's Proposed Findings of Fact). Aulton recognizes that the formulator must consider many factors when selecting a drug use form. According to Aulton:

> The formulation of drugs into dosage forms requires the interpretation and application of a wide range of information from several study areas. Whilst the physical and chemical properties of drugs and additives need to be understood, the factors influencing drug absorption and the "requirements of the disease to be treated also have to be taken into account when identifying potential delivery routes. The formulation and

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[12] Aulton, Pharmaceutics: The Science of Dosage Form Design (1988). Chapters 1 and 9 were submitted.

> associated preparation of dosage forms demands careful examination, analysis and evaluation of wide ranging information by pharmaceutical scientists to achieve the objective of creating high quality and efficacious dosage forms.

(Aulton, p. 12).

Due to these many variables, formulators perform in vitro/in vivo tests in order to understand the physical and chemical properties of the drug and how the drug will react in living beings. As a basic practice, a formulator knows that in vitro tests do not always track that which occurs in vivo. Hence, the careful formulator relies on in vitro testing only if verified by in vivo testing. Aulton writes:

> Dissolution rate data when combined with solubility . . . . provide an insight to the formulator into the potential in vivo absorption characteristics of a drug. However, in vitro tests only have significance if they can be related to in vivo results. Once such a relationship has been established, in vitro dissolution tests can be used as a quality control test.

(Aulton, p. 9).

For example, in this case, Dr. Tack determined to formulate drospirenone with an enteric coating solely based on in vitro tests. For four years he labored under the notion that an enteric coating was required. However, upon checking the absolute bioavailability of drospirenone by conducting an in vivo test without any enteric coating at the suggestion of his colleague Dr. Hümpel, he learned otherwise. Tack initially failed to follow the practice which Aulton adopts that in vitro testing is only valid if verified in vivo. If Tack conducted in vivo tests at the onset, then he would

have known drospirenone absorbs at a faster rate than it isomerizes, and therefore possessed good bioavailability.

The need for in vivo testing is also supported by the McGilveray article.[13] (DX 1004). In McGilveray, the author reviews a two-day workshop discussing in vitro dissolution of immediate release dosages. Regulators and industry personnel attended this high-level workshop. McGilveray reports on areas of consensus. One major area of consensus was "general lack of confidence of in vitro dissolution results . . . in the absence of an in vivo: in vitro correlation." (McGilveray at 1030). The workshop scientists also concluded that tablet formulation issues are simplified when a correlation exists between in vitro and in vivo measures (McGilveray at p. 1031). And at another point, McGilveray penned that the workshop professionals agreed that "in vitro/in vivo correlations . . . are rare" for immediate release products. (McGilveray at 1033). Accordingly, in vivo tests generally control. In addition to Aulton and McGilveray, the experts at trial generally acknowledge this methodology.

Dr. Chambliss (see bio at p. 9), Barr's expert, opined that in vivo testing is more informative to formulators than in vitro testing because it is done in the body and it directly demonstrates what happens in the body (1T, 63:19-23). One in vitro test is not predictive of what will happen in vivo (7T 97, 5 through 98, 6). Dr. McGinity (see bio at p. 8), Bayer's

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[13] McGilveray, Ph.D., *Overview of Workshop: In Vitro Dissolution of immediate Release Dosage Forms: Development of In Vivo Relevance and Quality Control Issues*, Drug Information Journal, Vol. 30, pp. 1029-1037 (1996).

expert, testified that one starts with in vitro testing, and then does in vivo testing (7T 105, 12-14). The prior art taught that only when in vitro tests actually correlate to in vivo results, then the in vitro results are considered significant (7T 106, 8-11). In most cases, one will not know if an in vitro dissolution test is what will occur in vivo until one performs in vivo testing (7T 98, 2-6). In vitro testing frequently does not correlate to in vivo testing (7T 98, 7-9). Despite the general rule, McGinity opined that this principle does not apply to acid sensitive drugs. McGinity, however, does not point to any prior art to support his point of view.

In this case, Bayer principally relies on Nickisch (see p. 57) which are not supported by an in vivo correlation. The Court concludes that the prior art teaches that a person of ordinary skill in the art would not rely on in vitro results where there is no correlation to in vivo tests. This makes sense because the formulators would need to know the parameters of the drug prior to determining dose form. It is similar to an engineer or architect who would verify topographical conditions and property lines before designing improvements to real property. It is as much a matter of common sense as it is prior art.

As discussed above, the prior art logically prompts person of ordinary skill in the art when considering formulation techniques, such as micronization or enteric coating, to perform in vitro and in vivo testing.

B. *Micronization*

Bayer asserts the first non-obvious aspect of the '531 Patent is that 2-4 mg of drospirenone could be micronized to increase its bioavailability. To the contrary, Barr argues that micronization of drospire-

none would be obvious to the person of ordinary skill in the art.

The general rule is that micronization will improve the dissolution of a poorly water soluble drug. Drospirenone is a poorly water soluble steroid (7T 4, 9-10; 7T 63, 20-24). Reducing particle size increases the rate of dissolution, causing more of the drug to be absorbed in the body (1T 40, 6-19; 7T 63, 4-6). The first step when formulating a poorly water soluble drug is to micronize the drug in order to improve its dissolution rate (1T 40, 6-8; 5T 20, 16-21; 7T 65, 23 through 66, 3). Dr. Chambliss contends that the prior art bears out this rule even with regard to drugs related to drospirenone (1T 44, 11-24). Citing to McInnes (JX 019),[14] Chambliss testified that micronization of spironolactone (Def. 20 at p. 7) led to improved bioavailability (1T 45, 3 through 48, 25).

Bayer on the other hand, states that drospirenone falls within one of the known exceptions to the rule. Drospirenone is an acid-sensitive drug. Bayer contends that the prior art teaches away from micronization to increase the dissolution rate of acid-sensitive drugs like drospirenone, even if the drug is poorly water soluble. To Bayer, the prior art teaches that micronization of an acid-sensitive drug without any protection from stomach acid will increase the extent of drug degradation. Thus, Bayer argues the prior art teaches away from micronization of unprotected drospirenone. In support of this teaching away, Dr. McGinity, citing Aulton, stated "[Y]ou reduce the particle size, increase the dissolution rate,

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[14] McInnes, *Effect of Micronization on the Bioavailability and Pharmacologic Activity of Spironolactone*, Journal of Clinical Pharmocology, Vol. 22, 410 (Aug.1982).

but you also increase the rate of degradation." (PTX 19, Aulton 1988 at 156; 7T 17, 11 through 18).

McGinity further contends that micronization can lead to agglomeration (Def. 2 at p. 4) of particles and thus decrease dissolution (7T 14, 23 through 15, 17). Chambliss counters that any cause of agglomeration is overcome through routine techniques (2T 84, 2; 3T 71, 13-16).

Aulton recognizes that one of the chief techniques a formulator uses to increase bioavailability of a poorly water soluble drug like drospirenone is the particle's size. Altering particle size is a means for overcoming drug limitations (PTX 19 at 7). By micronizing, there is an increase in surface area which leads to increased dissolution and improved absorption. Aulton emphasizes:

> Particle size reduction results in an increase in the specific surface (i.e. surface area per unit weight of powders). Drug dissolution rate, absorption rate, dosage form content uniformity and stability are all dependent to varying degrees on particle size, size distribution and interactions of solid surfaces. In many cases for both drugs and additives particle size reduction is required to achieve the desired physicochemical characteristics.
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> * * *
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> It is now generally recognized that poorly soluble drugs showing a dissolution rate limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided form with larger surfaces than as the coarse material . . . . The fine material often in micronized form with larger specific surface

dissolves at faster rates which can lead to improved drug absorption by passive diffusion.

Although the general rule is that micronizing increases dissolution rate, it is not always the case because the drug may become more unstable—"reduced chemical stability." (PTX 19 at 8). Sometimes extensive particle size reduction increases "the tendency of the particles to aggregate" which would decrease bioavailability. Aulton recognizes the uncertainty of reducing particle size of acid sensitive drugs. Thus, chemical degradation will be minimized if an acid-unstable drug does not dissolve readily in gastric fluids; or stated differently, micronization may increase the extent of drug degradation. This would result in a decrease in the amount of intact drug available for absorption (PTX 19 at 156).

Despite the warning about acid-sensitive drugs, Aulton also notes that there are exceptions to the rule like digoxin and spironolactone (1T 58, 3-14; PTX 19 at 156).[15] In addition to Aulton, there are a number of references to prior art concerning micronization of poorly water soluble drugs. They are reviewed below. One of those poorly water soluble sex steroids on which micronization assists in dissolution is progesterone.

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[15] Chambliss notes that Aulton states penicillin and erythromycin require enteric coating, but these are micronized presently (1T 55, 12-19; 7T 18, 24 through 19, 3). Bayer distinguishes digoxin. Specifically, digoxin is a heart drug with "a narrow therapeutic window" (Bayer's Proposed Findings of Fact at ¶ 230; DX 37); and according to McGinity, a physician has more flexibility in dosing a patient (7T 47, 11-16). The parties dispute whether another acid-sensitive drug, etoposide, is enteric coated or not (3T 47, 22 through 48, 15 and 3T 79, 3-15).

In the Hargrove article,[16] the author sets out to determine whether particle size and vehicle (dosage form) could improve intestinal absorption of progesterone in order to increase its bioavailability. Previously, oral dose form of progesterone had proven ineffective. Hargrove used five different dosage forms including plain milled, micronized, and enteric coated progesterone. Six postmenopausal women and one man volunteered. Each subject was tested six times. Hargrove found that the optimal preparation for oral administration of natural progesterone is "micronization of the particles and dissolution in oils." He further found that the process of enteric coating to protect against gastric acidity did not increase absorption (DX 42 at 951). Hargrove teaches that "absorption of oral progesterone is influenced by vehicle and particle size; that "[m]icronized progesterone, in oil showed the highest average progesterone concentration . . . and the shortest time from ingestion to measured peak." (DX 42 at 948-949). Although the study does not specifically address drospirenone, it confirms that not all acid-sensitive drugs require enteric coating. In addition to Hargrove, there are at least two other articles that suggest micronization of poorly soluble drugs is appropriate.

In McInnes,[17] twenty-four men were administered two separate doses of micronized spironolactone two weeks apart. The result was that the micronized product demonstrably improved bioavailability.

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[16] Hargrove, *Absorption of oral progesterone is influenced by vehicle and particle size*, American Journal of Obstetrics & Gynecology., vol. 161, No. 4, Oct. 1989, pp. 948-951.

[17] McInnes, *Effect of Micronization on the Bioavailability and Pharmacologic Activity of Spironolactone*, Journal of Clinical Pharmacology, Vol. 22, p. 410 (Aug.1982).

McInnes noted "[t]he greater bioavailability of the micronized formulation reflected differences in the dissolution profiles of the spironolactone preparations . . ." and "[c]ompared to the standard preparation, micronization clearly leads to an improvement in the bioavailability of spironolactone . . . ." (JX 19 at 415).[18]

The Court concludes, and the experts agree that the prior art generally instructs that micronization may improve the dissolution of drospirenone (1T 40, 6-8; 5T 20, 16-21; and 7T 65, 23 through 66, 3). Undoubtably, there would be some concern about dissolution of a poorly water soluble acid sensitive drug, but the person of ordinary skill in the art would conclude that micronization is a viable option.

C. *Enteric Coating*

Bayer asserts that the second non-obvious aspect of the '531 Patent is that micronized drospirenone need not be protected from the gastric environment with an enteric coating. Barr argues that the prior art

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[18] In Chaumeil, the author reviews much of the literature concerning micronization of poorly soluble drugs being an impediment to bioavailability. The author concludes that "micronization improved their digestive absorption . . . bioavailability and clinical efficacy." (DX 461 at 211). More specifically, with regard to progesterone the author concluded that, "reducing particle size by micronization can improve the rate of dissolution of poorly soluble materials." (DX 461 at 215.) Chaumeil, J.C., *Micronization: A method of improving the bioavailability of poorly soluble drugs*, Methods Findings in Experimental Clinical Pharmacology Vol. 20, No. 3 p. 211, (1998). Lastly, in an article about bioavailability of sex hormones, Fotherby concurs that micronization improves solubility. Fotherby, K., *Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy*, Contraception, Vol. 54, p. 59 (1996).

taught the person of ordinary skill in the art that it was not automatically necessary to enteric coat acid-sensitive drospirenone.

The parties concede that immediate release and enteric coated formulations were both known in the prior art (5T 183, 21-23; 7T 96, 18-20). Generally, formulators use enteric coatings for two purposes: to protect a drug from degrading in the acidic environment of the stomach and to prevent stomach irritation (7T 24, 15-22; PTX 19). Due to drospirenone's acid sensitivity, Bayer argues that the formulator must protect drospirenone from isomerizing and the prior art taught formulators to employ an enteric coating (Bayer's Proposed Findings of Fact at ¶¶ 215-17). In support of this proposition, Dr. McGinity testified that enteric coatings do not ordinarily affect the amount of a drug that becomes bioavailable to the patient (7T 26, 15-17); and since enteric coatings do not add a step to the manufacturing process, they are commonly used. He noted that even immediate release formulations have a coating step (7T 25, 1-24). Accordingly, enteric coating a tablet containing a combination of drospirenone and ethinylestradiol would not pose any concern to the person of ordinary skill in the art (7T 27, 2-10).

Bayer's argument is supported by the United States Pharmacopeia, the National Formulatory (1995) (PTX 0184). It states in part:

> Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. The term "delayed release" is used for Pharmcopeial purposes, and

the individual monographs include tests and specifications for Drug Release (see drug release 724, p.1951).

In contrast, Barr asserts that enteric coating a drug is a complicated, expensive, and cumbersome manufacturing process that has inherent variability concerns, and as a result makes it a last resort for formulators dealing with an acid-sensitive drug (1T 54, 16 through 55, 8; 5T 25, 25-26). Inherent concerns with enteric coating include variability in bio-availability within the same patient and among different patients (5T 185, 2-5; 6T 9, 22 through 10, 3). This is known as inter- and intra-subject variability (5T 186, 4-10).

More specifically, an enteric coated tablet may empty in the stomach within minutes or within hours (1T 54, 16-22). Since the enteric coat is pH sensitive, it will not disintegrate in the stomach. Rather, delayed release enteric coatings are designed to disintegrate in the intestines (5T 21, 8-13). As long as an enteric coated drug is sitting in the stomach, the drug is not available to be absorbed, and the patient is not receiving any therapeutic effect (Def. 23 at p. 7) from the drug (1T 54, 23 through 55, 2).

The positions of Barr and Bayer are extremely polarized; the prior art is more centered. Aulton places the use of enteric coatings in the proper perspective. Aulton's textbook recognizes the necessity of enteric coating to the formulation of acid-sensitive drugs. Enteric coatings are "designed to resist gastric fluids [and] to disrupt or dissolve when the coated tablet enters the duodenum." (PTX 19 at 171). "Such delayed release provides a means of protecting drugs which would otherwise be destroyed if released into gastric fluid." (Aulton at 171). But then Aulton

advises the formulator about its drawbacks. First, he emphasizes that there are five common types of oral dose forms, including coated tablets. Such coated tablets have the least bioavailability (Def. 5 at p. 4). He writes:

> Thus the greater the number of intervening steps, the greater will be the number of potential obstacles to drug absorption and the greater the likelihood of that type of dosage form reducing the bioavailability exhibited by the drug. Hence, the bioavailability of a given drug tends to decrease in the following order of types of dosage form: aqueous solutions > aqueous suspensions > hard gelatin capsules > uncoated tablets > coated tablets.

(Aulton at 165).

In addition to the reduced bioavailability, Aulton notes that there are two principal drawbacks of using enteric coatings. They include a "significant delay in the onset of the therapeutic response of a drug, and . . . there is considerable intra-subject and inter-subject variations in the onset of therapeutic actions exhibited by drugs administered as enteric coated tablets." (Aulton at 171). Aulton cautions:

> Hence, coated tablets not only possess all the potential bioavailability problems associated with uncoated conventional tablets but are subject to the additional potential problem of being surrounded by a physical barrier. Enteric coated tablets, which are designed to remain intact in the stomach, are very erratic and this contributes to the unusually large intersubject variability found in the absorption of drugs from this type of dosage form. (Gibaldi, 1984).

(Aulton at 170)[.]

The issue of formulating an oral contraceptive is further complicated by therapeutic considerations. As Bayer argues, oral contraceptives must be over 99% effective and "one dose must fit all." Obviously then, inter- and intra-subject variability in bioavailability associated with enteric coatings becomes a significant obstacle to its use in formulation of an oral contraceptive.

Since inter- and intra-subject variability is a major disadvantage, Bayer's contention that the person of ordinary skill in the art would automatically be directed to enteric coat drospirenone is rejected. The person of ordinary skill in the art would not rule out formulating a micronized drospirenone without enteric coating in order to overcome variability concerns.

In summary of the general areas of prior art, the Court finds that the person of ordinary skill in the art would: (1) conduct in vitro/ in vivo testing for bioavailability of drospirenone; (2) conclude micronization of drospirenone is a viable formulation option; and (3) not rule out formulating drospirenone without an enteric coating.

These three conclusions must be considered in light of two specific references: Krause I, II, III, and Nickisch, as well as certain other prior art concerning the combination of drospirenone and ethinylestradiol. They are analyzed below.

D. *Krause I, II, and III*

Both parties mainly rely upon the studies and reports of Krause and Nickisch to support their respective positions on the obviousness of the '531 Patent claims. Each of these articles are considered prior art on both aspects of the '531 Patent claims

(micronized and non-enteric coating), and therefore are discussed at length.

Barr argues that the Krause studies, which primarily concern spirorenone (Def. 21 at p. 7), are the controlling prior art, and inform the person of ordinary skill in the art on the formulation of drospirenone with respect to both micronization and enteric coating.

In Krause I,[19] both an in vivo and an in vitro experiment were conducted. Each is discussed below (JX 4). In the in vivo experiment, two young adult males were given 10 mg spirorenone in tablet form. The subjects were also administered an aldosterone infusion and water during the test period. Blood samples were extracted from each subject at various intervals over a 12-hour period. The same procedure was repeated a week later, except the subjects were administered 40 mg of spirorenone in tablet form. Krause subjected the plasma samples to a chromatographic system known as the high performance liquid chromatography ("HPLC") and thin layer chromatography in order to identify the isomer (Def. 13 at p. 6) of spirorenone and to determine the rate of isomerization in the blood plasma of the subjects. The main purpose of the study was to establish a procedure for detecting concentrations for both spirorenone and its isomer in the blood; and secondly, if substantial amounts of the isomer were present in the blood plasma, whether there was a need to develop a "pharmaceutical formulation resistant to gastric

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[19] Krause *et al.*, *Determination of Plasma Levels of Spirorenone, a New Aldosterone Antagonist, and One of its Metabolites by High-Performance Liquid Chromatography*, Journal of Chromatography, 230 (1982) 37-45. (Krause I)

juice." (JX 4 at 37). The HPLC detection apparatus described in Krause I had a detection limit of less than 5 ng/ml (JX 4 at 37). Krause was unable to detect any isomers (Def. 13 at p. 7) of spirorenone in the blood plasma for either subject (JX 4 at 41 and 3T 149, 3-12). Krause I concludes that "[t]he lactone rearrangement product of spirorenone [the isomer] was not detectable in the plasma, suggesting that the absorption process may be faster than the acid-catalyzed isomerization of the drug."

The in vitro experiment of Krause I concerns drospirenone and spirorenone placed in a vial containing 0.1 N hydrochloric acid. According to Krause, a pH of 1 simulates the acid profile of the human stomach. This study was conducted in acid to investigate the isomerization rate of both drospirenone and spirorenone. The results of the experiment indicate that drospirenone and spirorenone have similar isomerization profiles in in vitro testing (1T 71, 19-23). Both were found to isomerize in acid. Krause found that 80% of the drospirenone and spirorenone converted into their isomers at 400 minutes (point of equilibrium). Krause found "the process of rearrangement was relatively slow compared to possible absorption rates in the stomach" as suggested by comparing the in vivo study with the in vitro results.[20] The primary conclusion of the author was that the HPLC method was sufficiently sensitive detection equipment for further clinical studies of spirorenone.

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[20] Although neither party argued same, Krause followed Aulton and McGilveray's basic rubric that studies must be conducted to determine an in [sic] in vitro/in vivo correlation. Krause did not find such a correlation with spirorenone.

In Krause II,[21] four Macaca Fascicularis monkeys were intragastrically (orally) administered 20 milligrams per kilogram of spirorenone in a microcrystalline suspension over 46 days. Blood samples were taken after doses 1, 8, 22, and 46 to identify even small amounts of isomers and metabolites (Def. 15 at p. 6) (Krause II; JX 6 at 63; 3T 156, 1 through 158, 9). A fifth monkey was given a dose (26.5 micrograms) of a radioactive form of spirorenone for eight days. Blood samples were taken after the last dose (4T 8, 12-10 through T10, 9-12). The purpose of the Krause II study was to detect the presence of isomers of spirorenone in Macaca Fascicularis monkeys when administered intragastrically (3T 156, 20-22). The pH of the stomach of a Macaca Fascicularis monkey in the fasted state is similar to the human stomach, about pH 1-3 (4T 7, 2-7). No isomer was found in the blood plasma.

Krause III[22] discusses another human study with spirorenone. This study involved thirteen subjects rather than two (as in Krause I in vivo). It used the same 10 mg and 40 mg doses of spirorenone in a non-micronized tablet as in Krause I (JX 5 at 232; 2T 5, 4-8). Unlike Krause I, the subjects in Krause III did not drink a large amount of water during the study (JX 5 at 231). The primary aim of Krause III was to evaluate the "pharmacokinetics of spirorenone in healthy volunteers under normal conditions without

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[21] Krause *et al.*, *Isolation and Identification of Spirorenone Metabolites from the Monkey* (*Macaca Fascicularis*), Steroids, vol. 40, No. 1, pp. 81-90, July 1982 (Krause II).

[22] Krause, *Pharmacokinetics of the New Aldosterone Antagonist, Spirorenone, in Health Volunteers after single does* [sic] *and repeated daily doses*, European Journal of Clinical Pharmacology (1983). (Krause III).

an aldosterone infusion or an oral water load." The parties agree that the Krause III in vivo study is more powerful than the Krause I in vivo study because more subjects were included, and the drug was administered over a longer period of time (2T 5, 4-23).

This study, like the other in vivo Krause studies, found no isomer in the plasma. Krause III postulated that incomplete absorption might have occurred due to the high dose (40 mg), which is expected "in view of the low aqueous solubility of the drug molecule."

In the broadest terms, according to Barr, Krause I, II, and III stand for the proposition that spirorenone and drospirenone are related drugs; as such the person of ordinary skill in the art would recognize that drospirenone and spirorenone would isomerize in vitro but absorb in vivo. Bayer frontally assaults this proposition on four grounds. These grounds are discussed below.

First, Bayer posits that since the Krause studies primarily concern spirorenone as opposed to drospirenone, the person of ordinary skill in the art would not rely on such studies when formulating drospirenone because they are unrelated. Barr argues the two drugs are closely related. The evidence is:

1. drospirenone and spirorenone are both acid sensitive, and isomerize at similar rates in vitro (7T 112, 7; 3T 144, 24 through 145, 1; 1T 71, 19-23);
2. both are steroids (7T 112, 5);
3. drospirenone and spirorenone are derivatives of spirolactone (7T 111, 10-11);

4. both have same chemical structure but for one chemical bond at one location;

5. Dr. Tack acknowledged the substances are related but for one chemical bond at one location (JX 4; 1T 61, 20 through 62, 2);

6. the steroids have the same pharmacological properties (7T 115, 15-25); and

7. Nickisch (see p. 57) referred to the drugs as being in the same "family of substances" of synthesized steroids (JX 003).

The Court concludes that the person of ordinary skill in the art would find the drugs are closely related (about as close as fraternal twins) and would assess these studies when formulating drospirenone.

Second, Bayer argues that since the steroids have different therapeutic (Def. 23 at p. 7) purposes (drospirenone is a contraceptive and spirorenone is a diuretic), Krause I, II, and III would not be instructive to a person of ordinary skill in the art in formulating drospirenone. Dr. McGinity testified that a formulator must take into account the therapeutic use of the drug (6T 64, 11-24). McGinity reasoned that the threat of drug degradation is a major factor to consider when formulating an oral contraceptive; but it is far less important in the case of non-contraceptive indications (6T 68, 1-16). Dr. Bhavani and Dr. Pramar (see bios p. 10) are in accord (4T 43, 1-4). Dr. Pramar concluded that therapeutic use is "one of the factors the formulator looks at." (5T 38, 9-11). The only witness differing opinion is Dr. Chambliss, who saw no reason to consider therapeutic use because "the formulator's job is to get either one of those drugs into the bloodstream as they can . . . have their pharmacological benefits." (1T 72, 16-21).

Aulton's hornbook teaches that therapeutic indication is an important factor in the design of dose form. He instructed "the nature of the disease or illness against which the drug is intended is an important factor when selecting" dosage form (PTX 11 at 11). The Court concludes that the person of ordinary skill in the art would take into account the different therapeutic uses of the steroids.

Third, Bayer argues that the drug dosage amount of spirorenone used in Krause studies, as compared to the usual dose of drospirenone, is immensely different thus rendering the Krause studies worthless. In Krause II, the dosage of spirorenone varied from 10 mg/kg to 40 mg/kg whereas the dosage amounts of drospirenone when used as an oral contraceptive is far less: 2-4 mg (5T 106, 24 through 107, 7; 6T 105, 22 through 106, 7).[23] The Court finds that the person of ordinary skill in the art would recognize that drug dose amounts may affect the outcome of the studies (Aulton PTX 11 at 11).

Fourth, Bayer claims that Krause III should be discarded because the recipients were not given an oral water load similar to Krause I, thereby reducing the amount of spirorenone that could possibly

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[23] At trial, there was much ado about the dose quantity given to the fifth monkey in the Krause II study. Barr's witness, Dr. Bhavani testified that even if Bayer was correct that the drug quantities of spirorenone were so large they affected isomerization, the fifth monkey received a small dose of spirorenone that was laced with radioactive material and there was no evidence of isomerization (4T 9, 24 through 10, 15). McGinity relies on an internal report of Bayer to establish that the drug dosage given to the fifth monkey was significantly higher than the study reported (6T 106, 18 through 19, 9). As noted earlier, the internal reports are suspect and this particular report was not clearly linked to this study.

dissolve (Def. 7 at p. 5) in the stomach (7T 161, 3-14). McGinity testified that the subjects imbibed less water, and since spirorenone is poorly water soluble (6T 94, 25 through 95, 21), it stands to reason the rate of dissolution would decrease. Bayer claims that this evidence is unrebutted (Bayer's Proposed Findings of Fact at ¶ 287). That is not true. Barr's argument is that Krause III confirms the findings of Krause I in vitro, that spirorenone is absorbed quickly, and is a more "powerful" study because there are more test subjects and test conditions were more realistic (the water load condition was substantially reduced) (4T 13, 20 through 16, 19).

The Court concludes that the person of ordinary skill in the art would recognize that water volume may impact the outcome of the dissolution rates, just as what and when a person has eaten affects gastric emptying times (see p. 10). Water overload would also be a factor. Although this Court agrees with Bayer that the therapeutic use, oral water load, and dose amount would be factors in determining formulation, the Krause references are not so distinguishable that the person of ordinary skill in the art would discount them entirely. Based on the above, the Court finds that the person of ordinary skill in the art would consider drospirenone and spirorenone are closely related steroids, and therefore drospirenone, like spirorenone may absorb in vivo, but isomerize in vitro. Due to the differences in drug dose amount, water load and therapeutic use, the person of ordinary skill in the art would perform independent in vitro/in vivo testing.

Fifth, Bayer asserts that the detection equipment (HPLC) (see p. 51) used to identify spirorenone and its isomer in the plasma of the subjects was not

sufficiently sensitive to identify any isomer below 5ng/ml. As a result, the isomer may have existed below this level. Therefore, it can not be determined to any degree of certainty whether spirorenone isomerized or absorbed at these lower levels (6T 98, 9 through 99, 9). Due to the limitations of the detection equipment, Bayer espouses that Krause is a poor reference which the person of ordinary skill in the art would not give much weight. This is an absurd conclusion. The most probable conclusion of a person of ordinary skill in the art, assuming Bayer's proposition is true, is that the testing must be replicated using the appropriate detection equipment in a manner consistent with the therapeutic use of drospirenone.

In conclusion, the Court finds that the person of ordinary skill in the art would consider Krause I, II, and III as a whole because spirorenone and drospirenone are closely related drugs. They act as a basis for the person of ordinary skill in the art to (a) determine that micronization may be an appropriate technique to utilize (Krause II); and (b) that it would be reasonable to perform independent bioavailability tests to confirm that drospirenone, like spirorenone, absorbed in vivo.

E. *Nickisch Study*

The parties concede that Nickisch[24] teaches that drospirenone isomerizes when exposed to hydrochloric acid in vitro. In Nickisch, drospirenone was incubated in hydrochloric acid for three hours at room temperature. At that point, it reached its

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[24] Nickisch K et al., *Acid catalyzed rearrangements of 15-beta 16-beta methylene-17-alpha-pregnene-21 17-carbolactone derivatives*, Tetrahedron Letters, Vol. 27, No. 45, pp. 5463-66 (1986).

equilibrium point; that is, drospirenone converted into an 8:2 mixture (8 parts isomer to 2 parts drospirenone). Bayer argues that Nickisch teaches away from exposing drospirenone to the gastric juices in the stomach because it would most likely isomerize in the stomach based on this in vitro test. Barr disagrees and attacks Nickisch on four grounds.

First, Nickisch is solely an in vitro study and the person of ordinary skill in the art would not entirely rely on Nickisch due to the absence of an in vivo correlation. The Court agrees (see p. 39).

Second, Barr discounts the study because the hydrochloric acid had a pH 1. This condition is the most extreme acid condition known to exist in the human stomach. Generally Barr maintains the stomach has a pH of greater than 1. Accordingly, the in vitro test is unrealistic, and even if true, isomerization, if at all, would occur at a substantially slower rate as the pH level rises. At trial, there was considerable testimony concerning the factors which may alter the acidity of the stomach at any given time. Generally, acidity is affected by what, when, and how much a person has eaten (7T 81, 4-23; 3T 147, 11-22); and the pH level of the stomach varies within a range of 1-3.5 (3T 65, 3-10). Aulton states:

> The pH of the fluids varies considerably along the length of the gastrointestinal tract. Gastric fluid is highly acidic, exhibiting a pH within the range 1-3.5. The fluid in the small intestine is generally considered to have a pH in the range 5-8, generally from a pH range of 5-6 in the duodenum to about pH 8 in the lower ileum. The fluid in the large intestine is generally considered to have a pH of about 8. Considerable variations within the above pH ranges may occur

in an individual. For instance, there appears to be a diurnal cycle of gastric acidity, the fluids becoming more acidic at night and fluctuating during the day primarily in response to food ingestion. Gastric fluid pH generally increases when food is ingested and then slowly decreases over the following few hours. There is also considerable intersubject variation in gastrointestinal pH depending on such factors as

1. The general health of the individual;
2. The presence of localized disease conditions (e.g. gastric and duodenal ulcers) along the gastrointestinal tract;
3. The types and amounts of food ingested; and
4. Drug therapy.

The Court concludes that a person of ordinary skill in the art would accept that the pH 1 condition simulates the stomach; because an oral contraceptive must be 99% effective, this requires the drug to function as intended even in this extreme circumstance.

Third, Barr argues Nickisch is of questionable value as prior art because drospirenone isomerizes at a very slow rate, and would empty from the stomach prior to isomerization. In order to determine the validity of this argument, one must compare two factors—rate of isomerization with the gastric emptying time.

With regard to the rate of isomerization, Nickisch found that drospirenone converted into 8 parts isomer and 2 parts drospirenone within 3 hours. McGinity testified that it would isomerize much quicker in the stomach because chemical reactions

accelerate at higher temperatures, and these chemical reactions occur more rapidly at first and then taper off. Here, McGinity concluded that since body temperature is about 17 degrees Celsius warmer than room temperature, isomerization would occur 2-3 times faster, or in terms of half life, within 30-45 minutes (6T 72, 21 through 73, 25). Barr refutes McGinity's calculation by arguing there is insufficient information provided by Nickisch to determine what the isomerization rate would be in the stomach, if it occurred.

The prior art supports McGinity's opinion that heat increases chemical reaction times. Martin[25] (PTX 0138) states:

> A number of factors other than concentration may affect the reaction velocity. Among these are temperature, solvents, catalysts and light. The speed of many reactions increases about two to three times with each 10 degree rise in temperature.

McGinity aggressively applies Martin, and adopts Lipp's declaration to conclude that the half life of drospirenone in the stomach is between 30 and 45 minutes (6T 73, 18-25). This isomerization time period must then be compared to the gastric emptying time to determine whether drospirenone would have most likely isomerized in the stomach based upon the Nickisch in vitro test.

As expected, the experts disagreed. Chambliss indicated that the gastric emptying time is as short as 14 minutes (3T 64, 1-6); McGinity stated that the gastric emptying time for liquids has a half life of 30

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[25] Martin, Physical Pharmacy (Lea & Febiger 1993).

minutes (6T 76, 2-19), and that some small particles have an emptying time of 2.0 hours (PTX 140 at 889).

There is considerable prior art on the subject. Generally, the literature notes that gastric emptying time varies. (PTX 19 at 146). Gastric emptying rate is influenced by a large number of factors such as hunger, anxiety, the patient's body position (i.e. lying on the right side), the intake of liquids, and antiemetic drugs (e.g., metocloramide) (Gibaldi, 1984).

In another textbook, Wilson[26] concludes that "gastric emptying times show considerable variation both between subjects and according to the testing method used." (PTX 18 at 56). He writes:

> The motility patterns which are responsible for gastric emptying time depend upon the nature and frequency of food intake and therefore are extremely variable within and between individuals. Under the normal conditions in which food intake is not controlled, gastric emptying of orally administered formulations is unpredictable which can lead to erratic bioavailability (PTX 183 at 46).

Another commentator on the subject concurs.[27] Davis observed that gastric emptying time of the stomach varies due to certain factors including, but not limited to, whether the subject is in a fasting state, nature of dose form, etc. (PTX 140 at 887). Davis found in part,

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[26] Wilson, Physiological Pharmaceutics Biological Barriers to Drug Absorption, (Halstead Press, 1989)

[27] Davis, *Alimentary tract and pancreas Transit of Pharmaceutical dosage forms through the small intestine*, Gut, Vol. 27, 886-892 (1986).

> If a drug is absorbed exclusively from the small intestine there is a good chance that the time the delivery system spends in that region could be as short as one to two hours. Thus efficient disintegration of the dosage form and dissolution of the drug in the stomach could be a considerable advantage, if the stability characteristics of the drug so permit. In contrast, an over effective delay of a drug release such as enteric coating, could result in markedly decreased biological availability. (PTX 140 at 891).

In short, Bayer contends that when the half life of the isomerization rate of drospirenone (30-45 minutes) is compared to the gastric emptying time (1.5 hours), one must conclude that drospirenone would isomerize in the stomach.

Barr, on the other hand, states that Nickisch would simply conclude that isomerization occurs "within 3 hours" and since gastric emptying time can be as short as 15 minutes, little if any isomerization of drospirenone would occur.

The Court disbelieves both parties and their experts and concludes that the person of ordinary skill in the art would find that both isomerization rate and the gastric emptying time vary. Whether drospirenone absorbed or isomerized requires verification through precise in vivo and in vitro testing.

Fourth, Barr discredits Nickisch because its testing protocols about isomerization are virtually unexplained. That is, Nickisch refers the reader to a one-sentence footnote ("3. G. Raptis, personal communication") for his testing protocols. The text of Nickisch states in pertinent part:

isomerization occurs, provided the result that this is an acid-catalyzed reaction. Thus, *1* could be converted into an 8:2 mixture of *2* and *1* by treatment with 0.1N hydrochloric acid at room temperature within 3 hours.[3]

The same mixture is obtained if *2* is treated under identical conditions. The product-ratio 8:2 of compounds *2* and *1* thus represents the thermodynamic equilibrium of the acid-catalyzed isomerization. This rearrangement can be explained

Barr's expert, Pramar characterizes Nickisch as a "weak reference" (5T 27, 4-20). According to Bhavnani, the Nickisch article does not provide the necessary pertinent information regarding the drospirenone in vitro study, such as the amounts of drospirenone and 0.1 N HCL used in the study (4T 26, 17 through 27, 8); nor does Nickisch give any indication of the type or sensitivity of the detection method used to determine how much of the isomer was formed in the acidic media after three hours (7T 77, 25 through 78, 8). The Nickisch article only refers to a study done at a single pH value and reports the ratio of isomers at a single point of three hours, which does not permit computation of a rate of isomerization, or what would happen under the various pH values in the stomach and intestines (5T 27, 22 through 28, 4). It is

impossible to determine from the Nickisch reference how quickly the isomerization reaction occurred (5T 28, 4-8).

McGinity retorts that "personal communications are common in the scientific literature" (6T 76, 24 through 77, 15) so this footnote is adequate.[28]

Bayer misses the point. The problem is not the reference to G. Raptis, per se. It is the lack of details regarding the protocol of the study that is at issue. The Court finds the person of ordinary skill in the art would recognize that Nickisch establishes that drospirenone isomerizes in vitro, but would be alerted to the study's shortcomings.[29]

F. *Other Prior Art*

There are two other articles, two patents, and one patent application contained in the prior art which recognize that drospirenone and ethinylestradiol could be combined as an oral contraceptive. The two articles were authored by Dr. Oelkers, who had a professional relationship with Bayer.

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[28] Bayer also counters that there is a similar footnote in Krause I in vitro; but a review of it also indicates it is an easily distinguishable situation.

[29] On close examination, Barr also asserts the rate of isomerization is about the same in Nickisch as it is in Krause I in vitro. In Krause I in vitro, the equilibrium point of isomerization (8:2 mixture) is at 400 minutes. In Nickisch, the same mixture was reached at 180 minutes. Bayer concluded that the difference between these equilibrium points is due to the fact that slower dissolving particles were used in Krause I in vitro. Relying on an internal study, in Krause I, McGinity observes that the drospirenone was "evaporated to dryness," that is, converted to a solid (PTX 008). According to McGinity, a solid would dissolve slower.

In 1991, Dr. Oelkers published research regarding the effects of drospirenone on ovulation and its antialdosterone (Def. 3 at p. 4) effect (JX 009). In Oelkers I,[30] the author studied twelve healthy women who were split into two groups. The purpose of the study was to determine whether drospirenone would be a "suitable partner of ethinylestradiol" as an oral contraceptive due to its antialdosterone effect. Oelkers theorized that the use of drospirenone may prevent sodium retention and a rise in blood pressure in susceptible women. The study had some moderately positive results. Oelkers concluded "drospirenone may constitute an oral contraceptive with favorable effects on sodium status and blood pressure" (JX 009 at 842). The article does not mention isomerization, micronization, or enteric coating.

Again in 1995, Oelkers reports on a study of twenty women using drospirenone in combination with ethinylestradiol as an oral contraceptive[31] (JX 8). The study concludes that this combination is "remarkable in its ability to slightly lower body weight and blood pressure." There is nothing in the study which explains how the tablets were formulated, i.e. micronized and/or enteric coated.

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[30] Oelkers et al., *Dihydrospirorenone, a New Progestogen with Antimineralocortcoid Activity: Effects on Ovulation, Electrolyte Excretion, and the Renin-Aldosterone System in Normal Women*, Journal of Clinical Endocrinology and Metabolism, vol. 73, No. 4, 837-42 (1991) (Oelkers I) (JX 9).

[31] Oelkers, *Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism*, Journal of Clinical Endocrinology and Metabolism, vol. 80, No. 6. (1995) (Oelkers II) (JX 8).

The other prior art includes:

(1) The Spona Patent (DX 456) (see p. 19), wherein the inventor combined drospirenone and ethinylestradiol in a manner "completely analogously as it is already known for usual oral contraceptives with a 21-day intake";

(2) The Gast application (DX 55), wherein the patentee stated the "preferred daily dosage" was the combination of drospirenone and ethinylestradiol "admixed together" using "conventional methodology"; and

(3) The Lachnit Patent, wherein one of the "preferred embodiments" is a combination of ethinylestradiol and drospirenone, formulated "completely analogously to the way already known for oral contraceptives."

In short, from this prior art, a person of ordinary skill in the art would recognize that drospirenone in combination with ethinylestradiol would be formulated by conventional methods as an effective oral contraceptive.

Based upon specific references of Krause I, II, and III and Nickisch, the Court finds that the person of ordinary skill in the art would have known (1) that in vitro/in vivo studies of drospirenone are essential; and that such testing would have shown that drospirenone absorbs rather than isomerizes in the stomach; (2) micronization is an option with a poorly water soluble drug like drospirenone; and (3) enteric coating may be suspect due to inter- and intra-subject variability.

4. *Differences between the Prior Art and the Claims under Graham*

In order to apply the prior art to the claims, two legal principles come into play. They are the concepts of teaching away (Def. 22 at p. 7) and considering the prior art as a whole. As previously stated, Bayer argues that the prior art teaches away from micronization and immediately releasing drospirenone in the stomach. Generally, a reference is said to teach away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from the path set out in the prior art or led in a direction divergent from the path taken by the applicant. *See In Re Gurley*, 27 F.3d 551 (Fed.Cir.1994); *see KSR*, 127 S.Ct. at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966)).

In *In re Gurley*, the claimed invention was an epoxy-based printed circuit material that is bendable. There was another reference, Yamaguchi, which was a patent for a similar circuit board, except it used a polyester-imide resin instead of epoxy. Yamaguchi referred to circuit boards using epoxy as "inferior" to the polyester boards. Gurley argued his epoxy board was patentable because Yamaguchi taught away from using epoxy. In rejecting Gurley's argument, the Court of Appeals noted that epoxy boards were known in the art; and the mere fact that the Yamaguchi reference referred to epoxy boards as "inferior" is insufficient to say that Yamaguchi taught away from use of epoxy. Accordingly, the nature of the prior art that is teaching away is "highly relevant and must be weighed in substance." *In Re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994); *see generally*, *Ecochem, Inc. v. S. Cal. Edison*, 227 F.3d 1261, 1379-80 (Fed.Cir.2000).

In *Adams*, a companion case to *Graham*, the inventor created an electrical battery comprised of magnesium and cuprous chloride electrodes that utilized water for battery fluid rather than acid. *Adams*, 383 U.S. at 42. The government, after initially denying the effectiveness of the battery, began manufacturing versions of Adams's battery without compensating him. Adams sued for patent infringement. *Id.* at 45. The government alleged that Adams's battery was not patentable because "it represented either no change or an insignificant change as compared to prior battery designs." Adams argued that the prior art taught away from using water as a battery fluid and the fact that it worked "wholly unexpectedly, . . . showed certain valuable operating advantages over other batteries." *Id.* at 48.

Under such circumstances, the Court decided that the water-operated battery was nonobvious. *Adams*, 383 U.S. 51-52. The *KSR* Court looked approvingly on such an application of the teaching away doctrine, noting when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *KSR*, 127 S.Ct. at 174.

It is hornbook law that when evaluating the teaching away doctrine, the Court does not look at the single reference but considers the prior art as a whole. Here, this Court shall follow *Adams*, where there were a number of references regarding batteries using acid as fluid, and the Court considered them all. *Adams*, 383 U.S. at 45-48; *In Re Gurley*, 27 F.3d at 553. *See Takeda Chem. Indus., Ltd. v. Alphapharm Py., Ltd.*, 492 F.3d 1350 (Fed.Cir.2007), *pet. for cert. filed* 75 U.S.L.W. 3374 (Dec. 20, 2007) (No. 07-838); *In Re Gorman*, 933 F.2d

982, 986 (Fed.Cir.1991); 2-5 Chisum on Patents § 5.04) (wherein it concludes prior art must be viewed in its entirety). With these principles in mind, the differences, if any, between the prior art and the claims at issue are discussed.

The two claims in issue are (a) whether to micronize drospirenone so as to increase its bioavailability; and (b) not to protect the drospirenone from the acidic environment of the stomach.

At the outset, the person of ordinary skill in the art knew at the time of this invention that drospirenone and ethinylestradiol could be combined or admixed together using conventional methodologies to form an effective oral contraceptive (Oelkers, Spona, Gast, Lachnit). With regard to micronization of drospirenone, the prior art acknowledges that micronization is a common or conventional formulation technique to increase absorption and bioavailability (Aulton). Bayer argues that acid-sensitive drugs are an exception to this tenet, and as a result, the drug may suffer further degradation. Although that is partially true, Krause I, II, and III show that a closely related drug, spirorenone, absorbed rather than isomerized. In addition, there are a number of references (Hargrove, McInnes, Chaumeil) which note that poorly water soluble sex steroids benefit from micronization. Hence, micronization of drospirenone is consistent with the prior art and is obvious.

The second claim is that the prior art teaches away from exposing drospirenone, an acid-sensitive drug, to the gastric environment without an enteric coating. The Court concludes differently. Generally, enteric coatings are used with acid-sensitive drugs, but such coatings have drawbacks. The chief drawback is inter- and intra-subject variability of

bioavailability (Aulton). Since oral contraceptives must be 99% effective, this becomes an insurmountable obstacle to using an enteric coating. Accordingly, the person of ordinary skill in the art would be led to an immediate release tablet. In addition, and as noted above, Krause I, II, and III concern a closely related drug, spirorenone, and it absorbed in vivo. Together, the prior art recognizes that drospirenone does not need an enteric coat.

There is one other principle that is clearly established in the prior art which defeats both claims. The prior art states the in vitro studies are unreliable unless they are correlated to in vivo testing (Aulton, McGilveray). Unlike Nickisch, a person of ordinary skill in the art would conduct such testing. Decisions about drug dose form are then made based upon the in vitro/in vivo testing. That is, the decision whether to micronize and/or enteric coat comes second. In this case, Bayer argues that the person of ordinary skill in the art would reverse this process ("put the cart before the horse"). This does not make sense. Justice Kennedy in *KSR* observed that in analyzing an obviousness defense, the court must use its common sense. *KSR*, 127 S.Ct. at 1732. In this instance, Bayer's alleged exception to the in vitro/in vivo correlation rule (that it does not apply to acid sensitive drugs) does not ring true. A person of ordinary skill in the art must precisely know and verify the characteristics and chemical reactions of a drug in order to evaluate its therapeutic value in humans. To follow McGinity's alleged exception for acid-sensitive drugs can only lead to sketchy, imprecise formulation results and an increased risk of injury to users.

5. *Secondary Considerations under Graham*

Lastly, Graham permits review of secondary considerations in reviewing an obviousness defense. Such items as "market success," "long felt but unresolved needs, etc." may be weighted. *KSR*, 127 S.Ct. at 1729-30. In this case, there was little or no testimony about such items like market success except by argument of counsel. Whether the '531 Patent is a successful product and whether its anti-acne and anti-bloating characteristics were unresolved needs, does not alter the Court's decision. Generally, the invention development path evidence may be considered as a secondary consideration; but as stated in a previous section, this evidence was not credible.

The claims of the '531 Patent were obvious.

6. *Obvious to Try*

As noted, in *KSR* the Supreme Court ruled that a patent claim may be obvious if the combination of elements was "obvious to try." *KSR*, 127 S.Ct. at 723-24. In this case, the testimony was limited to discussion about whether or not to employ two common formulation techniques micronization and enteric coating. As in *KSR* "there are a finite number of identified predictable solutions." *Id.* at 724. In this case, based on the prior art as a whole, micronizing and immediately releasing drospirenone was obvious to try.

7. *Conclusions*

"[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. *In re Longi*, 759 F.2d 887, 896 (Fed.Cir.1985). The person of ordinary skill in the art knew (1) the

combination of drospirenone and ethinylestradiol was an effective oral contraceptive (Oelkers); (2) the dosage amounts (DX 457); (3) that the combination should be admixed together; (4) in a "conventional" manner (DX 457); (5) that a closely related drug, spirorenone, absorbed rather than isomerized in the stomach (Krause I, II, and III); (6) that isomerization data (Nickisch) was not confirmed in vivo; (7) enteric coatings are associated with inter- and intra-subject variability (Aulton); and (8) that bioavailability as a general rule is improved by micronization (Aulton). With this data, the person of ordinary skill in the art would have concluded that a bioavailability test should be undertaken which, as it is now known, would have confirmed that drospirenone absorbs and is bioavailable; or alternatively, there were limited finite choices for delivery of the oral contraceptive and micronized, immediate release tablets were obvious to try.

Therefore, all the asserted claims of the '531 Patent are obvious.

VII.

PRIOR PUBLIC USE

Barr separately maintains that the '531 Patent is barred by a prior public use pursuant to 35 U.S.C. § 102(b). According to § 102(b), a patent is rendered invalid if "the invention was . . . in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." There is no dispute that the Critical Date (Def. 6 at p. 6) for this analysis is August 31, 1998, as the '531 Patent application was filed one year later on August 31, 1999.

Barr contends that the U.S. clinical trial was both a non-experimental and public use of the formulation that become the '531 Patent (Barr's Proposed Findings of Fact at p. 89). Bayer maintains that the U.S. clinical trial was an experimental use, that was confidential rather than public (Bayer's Proposed Findings of Fact at p. 92).

There is no dispute that a "'public use' for the purposes of barring access to the patent system is a use more than one year before the patent filing date, whereby a completed invention is used in public, without restriction and in circumstances other than 'substantially for the purposes of experiment.'" *Allied Colloids Inc., v. Am. Cyanamid Co.*, 64 F.3d 1570, 1574 (Fed.Cir.1995); *see also New Railhead Mfg. Co. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1297 (Fed.Cir.2002), *cert. denied* 537 U.S. 1232, 123 S.Ct. 1357, 155 L.Ed.2d 196 (2003).

If a patent challenger makes a prima facie showing of public use, the patentee may negate this showing by demonstrating that the use of the invention was experimental. *Lough v. Brunswick Corp.*, 86 F.3d 1113, 1120 (Fed.Cir.1996), *cert. denied*, 522 U.S. 806, 118 S.Ct. 43, 139 L.Ed.2d 11 (1997). Both the public use and experimental use determinations are questions of law, in which the challenging party must prove the questions of fact by clear and convincing evidence. *Tone Bros., v. Sysco Corp.*, 28 F.3d 1192, 1197 n. 3, n. 4 (Fed.Cir.1994), *cert. denied* 514 U.S. 1015, 115 S.Ct. 1356, 131 L.Ed.2d 214 (1995). The Patent Act endows patents with a presumption of validity. *See* 35 U.S.C. § 282. "[T]he burden of proving invalidity always remains with the party asserting invalidity; the burden never shifts to the patentee."

Harrington Mfg. Co. v. Powell Mfg. Co. 815 F.2d 1478, 1482 (Fed.Cir.1986).

The law recognizes that an inventor may test his invention in public without incurring the public use bar. "Experimental use negates public use; when proved, it may show that particular acts, even if apparently public in a colloquial sense, do not constitute a public use within the meaning of section 102." *Baxter Int'l Inc., v. Cobe Labs. Inc.*, 88 F.3d 1054, 1059, (Fed.Cir.1996) (citing *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d 965, 971 (Fed.Cir.1984)), *cert. denied*, 469 U.S. 826, 105 S.Ct. 108, 83 L.Ed.2d 51 (1984). However, a public use does not require that the invention be discerned by an observer. *New Railhead Mfg. Co.*, 298 F.3d at 1297.

In determining whether there has been a public use within the meaning of section 102(b) the court looks to the totality of the circumstances. The totality of the circumstances is considered in conjunction with the policies underlying the public use bar. *Tone Bros., Inc.*, 28 F.3d at 1198. The circumstances may include: the nature of the activity that occurred in public; the public access to and knowledge of the public use; whether there was any confidentiality obligation imposed on persons who observed the use; whether persons other than the inventor performed the testing; the number of tests; the length of the test period in relation to tests of similar devices; and whether the inventor received payment for the testing. *Netscape Commc'ns Corp., v. Konrad*, 295 F.3d 1315, 1320 (Fed.Cir.2002). To determine whether there was a prior public use, the court also considers the following factors: (1) experimental use; (2) confidentiality; (3) control by the inventor. *Eli Lilly and*

Co. v. Zenith Goldine Pharm., 471 F.3d 1369, 1381 (Fed.Cir.2006).

Barr maintains that the Phase II and Phase III European clinical trials reduced to practice the '531 Patent invention, thus, the U.S. clinical trial could not be "substantially for the purposes of experiment." Further, Barr contends that the U.S. clinical trial lacked sufficient confidentiality and product restriction requirements with respect to the test subject, thus constituting a public use.

Barr's prior public use claim fails because they have not established by clear and convincing evidence that the U.S. clinical trial constitutes a public use of the '531 Patent one year before the Critical Date.

For a use to be invalidating under section 102(b) it must be public. Public use includes "'any [public] use of [the claimed] invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor.'" *Eli Lilly and Co., v. Zenith Goldine Pharm. Inc.*, 471 F.3d 1369, 1380 (Fed.Cir.2006) (quoting *In re Smith*, 714 F.2d 1127, 1134 (Fed.Cir.1983)). Barr maintains that Bayer failed to establish the necessary confidentiality and restriction requirements for the U.S. clinical trial. According to Barr, the following factors demonstrate a lack of confidentiality and control over the clinical trial: (1) the human patients knew they were taking an oral contraceptive composed of 3.0 mg drospirenone and .30 mg ethinylestradiol, in a blister pack form; (2) the informed consent did not contain confidentiality provisions barring the human patients from discussing the composition; and (3) there were no restrictions on the use of the test product, and some patients failed to return unused test product.

The parties agree that the Phase III U.S. clinical trial constitutes a use of the claimed invention in the United States before the Critical Date of August 31, 1998 (Barr's Proposed Findings of Fact at ¶ 213, Bayer's Response to Barr's Proposed Findings at ¶ 213). The Phase III U.S. clinical trial took place from December 9, 1996 through July 1998. The analysis was completed on February 10, 1999 (PTX 163).

Dr. Herman Ellman was the study manager for the U.S. clinical trial. As study manager he was responsible for creating and implementing all study protocols, including the confidentiality provisions, use restriction requirements and requirements for participation (JX 10 ¶¶ 14-24).

The patients met certain age, weight, and other health requirements before participating. (JX 10, Ex. E & H). Further, they agreed to monitoring by doctors both before, during, and after the study, and to maintain a daily diary noting whether the drug was taken correctly (JX 10 at ¶¶ 19-25, 36). Bayer maintained extensive records of these activities (8T 30, 31, 32).

Dr. Ellman also testified about the various confidentiality protocols employed during the U.S. clinical trial. Specifically Dr. Ellman described the confidentiality provisions directed toward the third parties who participated in running the trial (8T 12, 1-3; 23-26). Dr. Ellman testified that Bayer entered into confidentiality agreements with the principal investigators, who were responsible for recruiting subjects and performing the study according to the protocol (8T 23-26).

However, Barr focuses on the human patients rather than any other individuals participating in the

trial. Specifically, Barr cites to the fact that the human patients did not execute confidentiality agreements, and they were informed of the formula amounts for the drospirenone and ethinylestradiol. Barr notes that the only requirement for control was not to provide this drug to children. Finally the human patients were provided with several months of the study drug and some of that unused study drug was never returned (8T 31). Barr argues that this demonstrates that Bayer was not in control of the invention during the trial. Barr maintains that this lack of control indicates that the U.S. trial was public rather than confidential.

While Barr correctly argues that the existence of confidentiality agreements is a significant factor in the analysis, lack of confidentiality provisions for the human patients is not outcome determinative on the public nature of the use. *See, e.g., Astrazeneca AB v. Mylan Labs, Inc.*, (*In re Omeprazole Patent Litig.*), 490 F.Supp.2d 381, 508 (S.D.N.Y.2007); *see also Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 343 F.Supp.2d 272, 307 (D.Del.2004) (failure to use confidentiality agreements alone does not automatically result in a prior public use, a court must review other factors).

One, the court found the lack of a confidentiality agreement significant precisely because the inventor demonstrated his computer innovation to other computer personnel who could easily demonstrate the invention to others. *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1321 (Fed.Cir.2002). The *Netscape* court found that, unlike the instant action, the inventor failed to maintain any records, and permitted many individuals to use the invention without his oversight. *Id.* at 1321-22. The circums-

tances of *Netscape* are amply distinguishable from the Phase III U.S. clinical trial. *Id.* at 1321. Here the persons other than the inventor who participated in overseeing and observing the U.S. clinical trial, i.e., the principal investigators and study managers contracted with oversight, were all bound by confidentiality provisions.

In *New Railhead*, the court found that use of the patented method for a drill bit on a construction site on public land constituted a public use, because the inventor failed to maintain control over the patented method by demonstrating it publicly. *New Railhead Mfg. Co.*, 298 F.3d at 1298. Here, there is no allegation that U.S. clinical trial occurred in a public area.

In *Baxter*, the court found that the inventor used the centrifuge in a public [sic] with no limitation of confidentiality for any of the individuals who witnessed the centrifuge in action. This combined with the lack any experimental need for the testing was found to be a public use. *Baxter Int'l Inc. v. Cobe Labs., Inc.*, 88 F.3d 1054, 1059 (Fed.Cir.1996).

In *Lough*, the court found a non-experimental public use where the inventor, provided the prototype seal assembly for motor boats to at least five different individuals without any obligation of secrecy or confidentiality or any inquiry as to how the prototype performed. *Lough v. Brunswick Corp.*, 86 F.3d 1113, 1121 (Fed.Cir.1996). The court rejected the patentee's experimental argument finding that he knew the seal assembly worked for the intended purpose after he tested it successfully on his own boat for three months.

In each of the aforementioned cases the court found an absolute lack of any confidentiality obligations

imposed on any of the individuals who tested the proposed patent. The case at bar is distinguishable because the only participants who did not have a confidentiality obligation were the test patients, and all that was disclosed to them was the amount of drugs due to ethical obligations. *Id.* at 1119; *see also, Janssen Pharmaceutical N.V. v. Eon Labs Mfg., Inc.*, 374 F.Supp.2d 263, 276 (E.D.N.Y., 2004), *aff'd by* 134 Fed. Appx. 425 (Fed.Cir.2005). (found that even though patients did not sign confidentiality agreements during clinical trial of orally administered drug this did not indicate a public use in light of the confidentiality obligations on the doctors, and their lack of knowledge regarding formulation).

Finally, the *Eli Lilly* case cuts against Barr's argument that Bayer lacked control over the U.S. Clinical trial. 364 F.Supp.2d 820 (S.D.Ind.2005). While in *Eli Lilly*, the security and control over the clinical trials was highly restrictive, i.e., the patients lived in the clinic, it was conducted by Lilly personnel and had extensive security. The trial court rejected the contention that failing to execute a confidentiality agreement constituted a controlling factor on the public use inquiry. *Id.* at 912-13. The *Eli Lilly* court found that since the patients were never informed of the compound and were strictly monitored a confidentiality agreement was unnecessary.

Although, in the U.S. clinical trial, the patients were informed of the compound, they were not informed of the alleged innovation. This Court agrees that the *Eli Lilly* reasoning is applicable here, especially since Barr did not present any testimony to counter Dr. Ellman's statements that it would be unethical to bind the patients in the U.S. clinical trial with a confidentiality agreement. This Court is

persuaded by Dr. Ellman's testimony that it would be unethical to prevent patients, through confidentiality provisions, from instructing their physicians on the medicine they were taking. Even Barr's own expert Mr. Mossinghoff offered no opinion as to whether having confidentiality provisions would be unethical (4T 143, 6-9).

As part of the disclosure argument, Barr contends that a public use may still occur even when the invention is not readily apparent to the study subjects; accordingly, the fact that the patients did not know the formulation has no bearing on the inquiry. *See Minn. Mining & Mfg. Co. v. Appelton Papers Inc.*, 35 F.Supp.2d 1138, 1148 (D.Minn.1999). Barr presented no evidence that the test patients were aware of the alleged innovation, i.e., micronization or lack of an enteric coating. This argument is also unpersuasive in light of *Janssen*, where the court found that there was no disclosure of the invention where patients lacked knowledge of the formulation. 374 F.Supp.2d at 276.

Finally, Barr argues that the patients' failure to return the unused test product demonstrates a lack of control over the U.S. clinical trial. Barr fails to distinguish the *In re Omeprazole* decision which dealt with adequate control. The *In re Omeprazole* court found that the patentee maintained control over the test drug for gastrointestinal pain by monitoring the amount of the drug administered, imposing patients diary requirements, and dispersing the test drug based on the patients' diaries. 490 F.Supp.2d at 507-08. Barr argues that in the *In re Omeprazole* trial, the patients did not receive further doses of the trial drug unless the clinical investigators could assure their compliance and continued participation in the

study. While Barr argues this was not the case in the Bayer U.S. clinical trial, they have failed to present a single instance to counter Dr. Ellman's testimony that the U.S. protocols were similar (8T 30-32; JX 10 at ¶¶ 19-27, 36). Dr. Ellman testified that the patients were required to maintain a diary in which they would record, compliance with drug protocol. These records were reviewed by the principal investigators and the patients had to comply with doctors visits.

Barr has failed to meet their burden of clear and convincing evidence that the U.S. Clinical trial was public, and therefore is unable to establish a bar under § 102(b).

Assuming Barr had established that the U.S. clinical trial was a public use, their § 102(b) would still fail, as Bayer has successfully asserted that the U.S. clinical trial was experimental in nature.

A use may not be experimental if the invention at issue was reduced to practice. For a pharmaceutical composition, a reduction to practice occurs when an inventor "actually prepared the composition and knew that it would work." *Estee Lauder, Inc. v. L'Oreal S.A.*, 129 F.3d 588, 592 (Fed.Cir.1997). The *Estee Lauder* court noted that "when testing is necessary to establish utility, there must be recognition and appreciation that the tests were successful for reduction to practice to occur." *Id.* at 594-95. After this occurs, "further 'experimentation' may constitute a barring public use." *RCA Corp. v. Data Gen. Corp.*, 887 F.2d 1056, 1061 (Fed.Cir.1989) (finding that public use is not negated by experiments directed to tangential or unclaimed aspects of the invention).

Barr maintains that the Phase II and Phase III European clinical trials reduced to practice the '531 Patent invention, and as a consequence, the U.S. Clinical trial could not be "substantially for the purposes of experiment." (Barr's Proposed Findings of Fact at ¶ 97). Specifically, Barr relies on the Phase II European dosage trial, (Research Report 9693) arguing that Bayer knew from the results of this study that the formula of 3.0 mg of drospirenone and .30 mg ethinylestradiol inhibited ovulation. Relying on this study of 52 women over a three-month period, Barr contends that Bayer's inventors prepared a formulation that they knew would work for ovulation inhibition. The Phase II dosage trial found that in comparing dosages of 2.0 mg and 3.0 mg drospirenone combined with ethinylestradiol, each combination prevented ovulation. Dr. Heithecker specifically noted that the 3.0 mg version "should be developed further because an ovulation-inhibiting effect was demonstrable under the 3-mg-version in all cases examined." (DX 4 at 2). Moreover, Barr argues that Example 5 of the '531 Patent describes only the test results of this trial to support effectiveness claims.

Barr also relies on Bayer's internal 1995 Master Plan and the results of the Phase III European trials for the contention that the inventors knew the formulation of 3.0 mg drospirenone and .30 mg ethinylestradiol would work to inhibit ovulation. The 1995 Masterplan reviews prior unidentified clinical studies in which 3.0 mg of drospirenone appeared to be effective as an oral contraceptive. Further, it identifies that the driving purpose of developing drospirenone, as opposed to other progestins, was "additional benefits [for women] with PMS and acne." (DX 277 at p. 41).

The Phase III European trial also found that the drospirenone (3.0 mg) ethinylestradiol (.30 mg) combination, when compared to a popular patent known commercially as Marvelon®, both were effective as ovulation inhibitors. The Phase III European trial was conducted from December 1992 through April 1996 (DX 2; 2T 57, 5 through 58, 5). The Study Report AI51 states, "both medications were shown to be effective oral contraceptives." (DX 2 at p. 4).

On the other hand, Bayer maintains the U.S. clinical trial was experimental. Both Dr. Heithecker and Dr. Shulman testified that the U.S. clinical trials were necessary to determine whether the formula would be effective as an ovulation inhibitor in the U.S. population (9T 33-35; Heithecker Dep. 108:10-15). Citing to differences in each of the test populations, such as weight, smoking/alcohol habits, and ethnic backgrounds, both Drs. Heithecker and Shulman testified that they required confirmation that the '531 Patent would be effective in the United States as well as with the European population. Dr. Ellman also testified that during the United States clinical trials the Phase III European trial results were still being analyzed (Heithecker Dep. 106:22-107:7; 8T 35-36). The subjects in the European trials were over 90% Caucasian while in the United States, the study population was far more diverse. While Mr. Mossinghoff, testified that, based on the test results from the European clinical trials that he believed that the '531 Patent was reduced to practice, he also testified that the he did not have a scientific background (4T 80-90).

For the scientific and technical analysis he relied entirely upon Dr. Chambliss, who testified that he believed a reduction to practice occurred, however, he

failed to specify the reasons for this conclusion. Dr. Chambliss testified that he believed a reduction to practice occurred based on the results of the Phase II and Phase III European trials. According to Dr. Chambliss, the only reason for the U.S. clinical trial was for FDA approval. He did not address Bayer's contention that it was to address a diverse population. Dr. Chambliss discussed the studies with respect to Dr. Ellman's understanding of the studies—not the inventors. Thus, he did not explain his analysis with respect to the reduction to practice inquiry. Specifically with respect to the Phase II study results being used as part of Example 5 of the patent, Dr. Chambliss stated that the drug was known to be effective from this trial. However there is no discussion as to the need—expressed by Dr. Heithecker and Dr. Shulman—for results from a more diverse U.S. population. Without any discussion or explanation as to why Drs. Shulman and Heithecker's reasons were insufficient, Barr has not met by clear and convincing evidence, its burden in establishing a reduction to practice (2T 65, 66, 70-71).

In *In re Omeprazole Patent Litigation*, the court found that the patent challenger had failed to establish by clear and convincing evidence that a reduction to practice occurred where the inventors were still analyzing the results of the clinical trials before the critical date. 490 F.Supp.2d 381, 507 (S.D.N.Y.2007). The *In re Omeprazole* court found that a reduction to practice did not occur upon the conception and initial testing of the omeprazole formulation. Rather, the court ruled that the patentee's four clinical trials demonstrated a need to confirm the formulation's effectiveness. Based upon the expert testimony that all results needed to be analyzed before a finding of safety and efficacy, and noting that the patent holder

did not have the results from at least one of those clinical trials, the court found insufficient evidence to establish a reduction to practice by clear and convincing evidence.

While *Estee Lauder* states that a reduction to practice is evidenced by recognition and appreciation that the tests were successful, the ability to see that for the U.S. population, based solely on European studies remains to be seen, especially in light of Drs. Heithecker and Shulman's testimony.

Barr did not present any testimony to counter the statements of Dr. Shulman and Dr. Heithecker, or otherwise make this Court doubt their understanding that the U.S. clinical trial was necessary to determine effectiveness in the more diverse U.S. population. The extensive clinical testing demonstrates that there was a lack of confidence that the efficacy of the claimed invention could be based solely on the European trials.

The testing here indicates that the determination of whether the '531 Patent formula would be effective was still being determined, and Barr has not presented any evidence to counter the statements of Dr. Heithecker, Shulman, and Ellman. As a consequence Barr has failed to meet its burden of establishing a reduction to practice by clear and convincing evidence.

VIII.

INEQUITABLE CONDUCT

The doctrine of inequitable conduct is an equitable defense to a claim of patent infringement. *In re Metoprolol Succinate Patent Litig.*, 494 F.3d 1011, 1020 (Fed.Cir.2007). Inequitable conduct consists of two elements: (1) "affirmative misrepresentation of a material fact, failure to disclose material information,

or submission of false material information," and (2) "an intent to deceive." *Bd. of Educ. ex rel. Bd. of Tr. of FSU v. Am. Bioscience, Inc.*, 333 F.3d 1330, 1343 (Fed.Cir.2003). "Both elements of a conclusion of inequitable conduct, intent and materiality, are questions of fact and must be proven by clear and convincing evidence." *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1345 (Fed.Cir.2007).

As to the first element, information is considered material "if a 'substantial likelihood [exists] that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent.'" *Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed.Cir.1990) (citations omitted). Alternatively, information is material if "(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) It refutes, or is inconsistent with, a position the applicant takes in: (I) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability." 37 C.F.R. § 1.56(b).[32]

The second element, intent to deceive, "need not, and rarely can, be proven by direct evidence. It is most often proven by 'a showing of acts the natural consequences of which are presumably intended by the actor.'" *Merck & Co. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed.Cir.1989) (citations omitted). Stated differently, "[d]irect evidence of deceptive

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[32] Section 1.56(a) requires that "[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section."

intent is not required," and as such, intent to deceive is often gleaned from the totality of the facts and circumstances surrounding "the patentee's overall conduct." *Ulead Sys., Inc. v. Lex Computer & Mgmt. Corp.*, 351 F.3d 1139, 1146 (Fed.Cir.2003).

In analyzing an inequitable conduct defense, the Court must engage in a two-step analysis. In the first step, this Court "must determine whether the conduct meets a threshold level of materiality. The trial court must then also determine whether the evidence shows a threshold level of intent to mislead the PTO."[33] *Am. Bioscience, Inc.*, 333 F.3d at 1343. The second step, once materiality and intent have been established at the threshold level, requires the Court to weigh materiality and intent to "determine whether the applicant's conduct is so culpable that the patent should be held unenforceable." *Id.* In weighing these essential elements, courts often treat them as somewhat intertwined, in that, "when balanced against high materiality, the showing of intent can be proportionally less." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed.Cir.2003).

Barr asserts this affirmative defense in response to declarations submitted to the PTO by two scientists in support of the '531 Patent. Barr contends that Dr. Herman Ellman and Dr. Ralph Lipp engaged in inequitable conduct because of their allegedly misleading declarations supporting the '531 Patent, and therefore ask this Court to invalidate the patent.[34]

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[33] PTO refers to the U.S. Patent and Trademark Office.

[34] Pursuant to 37 C.F.R. § 1.56(a) (also known as Rule 56), "[e]ach *individual* associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing

1. *Dr. Ellman*

Bayer submitted the declaration of Dr. Herman Ellman in support of the '531 Patent on December 12, 2003. The declaration concerned prior public use and explained that there was a U.S. clinical trial of Yasmin® before the '531 Patent was filed. Bayer's attorneys drafted the declaration for Dr. Ellman because he did not work for Bayer at the time. Bayer sent Dr. Ellman a copy of the declaration for him to

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with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." (emphasis added). Subsection (c) of that regulation defines "individual[ ] associated with the filing or prosecution of a patent application" as "(1) Each inventor named in the application; (2) Each attorney or agent who prepares or prosecutes the application; and (3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application." Thus it is fairly clear that the duty of candor applies to individuals and not corporate entities.

The testimony of Bayer's patent procedure expert, Mr. Larry Nixon, reflected this interpretation of the rule. Mr. Nixon indicated that Rule 56 "make[s] it clear that the duty of disclosure in the Patent Office revolves upon individuals, that is, humans not corporate entities," and despite some ambiguity in past incarnations of the rule, the ambiguity "was removed in 1992 with this new rule where it's clear that the duty to disclose to the Office is a duty to disclose all information known to that individual to be material to patentability as defined in this section." (8T 91, 24 through 92, 9). As discussed further below, the Court found Mr. Nixon to be a credible and reliable witness. Thus, based on the language of the rule and the testimony of Mr. Nixon, in examining the elements on inequitable conduct, the Court focuses on the actions and intent of the individuals submitting the declarations—Drs. Ellman and Lipp—and not Bayer, itself.

review and sign. Barr alleges that the Ellman declaration was misleading because it did not disclose that the clinical trials had been conducted in Europe on over 2,700 women from 1992 to 1996 (8T 70, 6-13). Thus, Barr contends, Dr. Ellman engaged in inequitable conduct because the declaration omitted any reference to the European clinical trials[35] and inaccurately described the reason for the U.S. clinical trial. Barr also contends that Dr. Ellman's assertion that "only testing in humans, under actual use conditions, could determine whether the tested composition was safe and effective" was an express misrepresentation because, based on the European trials, Bayer already knew that the drug was safe and effective in humans as an oral contraceptive. In other words, Barr asserts that Dr. Ellman could not have accurately represented that the U.S. trial was experimental had he provided the information regarding the results of the European trials. All of this information, Barr alleges, is critical to a determination of prior public use.

Barr argues that a reasonable examiner would have considered the omitted information concerning the European trials material to the patentability of the invention (5T 6, 19 through 7, 3). Barr alleges

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[35] Barr concedes that, while the declaration itself makes no reference to the European clinical trials, exhibits to the declaration make references to some data from the Phase I and II European clinical trials. These references include pregnancy rates from the European clinical trials (2T 140, 17-23), the study protocol discussed in the European trials (Exhibits A and C to the declaration), and the investigator's brochure (Exhibit D to the declaration), which included efficacy data from the trials. Barr maintains, however, that nowhere in the declaration or exhibits thereto, does Dr. Ellman ever discuss the European Phase III clinical trials or its favorable results.

that Bayer and inventor Dr. Heithecker had concluded that the drug was a reliable and safe contraceptive according to results shown in Research Report 9693 (DX 4), the Masterplan (DX 277), and the AI51 Report (DX 2); these results are allegedly contrary to the statement in Dr. Ellman's declaration that Bayer lacked the information needed to determine whether the clinical study drug was safe and effective for its intended purpose (DX 2, 4, 277; 4T 107, 16 through 108, 25). Accordingly, since there had been an actual reduction to practice of the invention during the European clinical trials, Barr argues that the U.S. clinical trial could not be experimental and thus constituted a public use prior to the critical date (4T 90, 25 through 91, 11; 4T 91, 24 through 92, 3). According to Barr, Dr. Ellman's statement that the U.S. clinical trial was experimental was therefore false and misleading.

The Court finds that the first element of inequitable conduct—threshold materiality—is satisfied. As an initial matter, it appears as though Bayer's main opposition to Barr's claim of inequitable conduct is that Dr. Ellman did not possess the requisite intent to deceive the PTO—not that the information was immaterial. Bayer points out that Dr. Ellman did, indeed, include some information about the European clinical trials in exhibits attached to his declaration. Barr's own experts conceded that Dr. Ellman referenced the examiner to the European studies: he gave the examiner data on pregnancy rates from the European clinical trials in one of the exhibits attached to his declaration (2T 140, 17-23); the study protocol discussed the European trials (Exhibits A and C); and the investigator's brochure (Exhibit D) included efficacy data from the European clinical trials. If Bayer believed that this information was

immaterial, it would not have included any of it in its submissions to the patent examiner. Furthermore, it stands to reason that the prudent examiner would have considered prior clinical trials in Europe as a factor in deciding whether the U.S. clinical trial was experimental and thus not a public use prior to the critical date.[36] Therefore, the European trial data was material to the patent application.

However, the Court finds that Dr. Ellman lacked the requisite intent to deceive the PTO.[37] Looking at the totality of the facts and circumstances surrounding the submission of the Ellman declaration, there was no intent to deceive. Dr. Ellman was a truthful and forthright witness. Dr. Ellman testified that the purpose of his declaration was to give the PTO information about a potential § 102(b) public use—the U.S. clinical trial—and not any of Bayer's European clinical trials (8T 39, 1-4). Dr. Ellman testified that he believed in 2003, and still believes today, that the U.S. trial was confidential and

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[36] This determination is separate and apart from, and does not affect, this Court's finding of no prior public use. The trials, as noted above, were experimental given the diversity of the populations involved (European v. American women). Materiality and prior public use are different inquiries for different reasons.

[37] As noted above, Dr. Ellman did not draft the declaration. There was no testimony in this case as to who at Bayer actually drafted the declaration. As stated above, the duty of candor applies to *individuals*. However, considering the Court lacks enough information to know who at Bayer drafted the declaration, it must put the onus of the duty of candor on Dr. Ellman pursuant to section 1.56(c)(3), as Dr. Ellman was "substantively involved" in the prosecution of the patent (as the signor of a declaration in support thereof), and was "associated with" Bayer. The same goes for Dr. Lipp, as analyzed below.

experimental (8T 22, 18-23). Further, Dr. Ellman testified that he never considered the European trials in reaching his conclusion that the U.S. trial was confidential and experimental (8T 22, 24 through 23, 6).[38] The Court found Dr. Ellman to be a reliable, believable witness, and therefore trusts his testimony as being truthful.

Also, while the Ellman declaration itself did not mention the European trials, the exhibits attached thereto did disclose some (but perhaps not all) of the information from the European trials. Thus, Dr. Ellman was not attempting to hide the existence of the European trials from the examiner. Furthermore, Bayer's patent procedure expert, Mr. Nixon, testified that he thought Dr. Ellman didn't realize that the activities in Europe could have relevance to the question that was being raised. "He thought he was answering the question with regard to possible prior public use in the United States . . . . So what I don't see evidence of, that he or anyone preparing these papers appreciated the fact that possibly somebody could argue that what happened in Europe was a reduction to practice that would then cut off experimental uses in the United States." (8T 118, 12-22). The Court also found Mr. Nixon to be a credible,

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[38] Dr. Ellman testified as follows:

Q: Did you ever consider the European trial in reaching your conclusion that the U.S. trial was confidential and experimental?

A: No, I did not.

Q: Why not?

A: It seemed to me, and this still seems to me, that question is one that can be answered independently by examining the nature of the U.S. trial, how it was conducted.

reliable witness.[39] Thus, taking Mr. Nixon's and Dr. Ellman's testimony together, the Court believes that Dr. Ellman thought he was signing the declaration in order to express his view on prior public use in the United States (via the U.S. trials), and not Europe. While Dr. Ellman's apparent carelessness in his treatment of the declaration may be slightly damaging to his alleged lack of intent, it appears to the Court that his behavior was just that—carelessness—and not actual intent to deceive. Dr. Ellman conceded that he did not provide any feedback to the Bayer representative (8T 60, 24 through 61, 5), did not make any changes to the declaration (8T 61, 9-11), and did not attempt to verify the accuracy of the information provided in the declaration or confirm any dates or exhibits attached thereto (8T 61, 15 through 61, 24). Barr notes that "one should not be able to cultivate ignorance, or disregard numerous warnings that material information or prior art may exist, merely to avoid actual knowledge of that information or prior art." *FMC Corp. v. Hennessy Indus., Inc.*, 836 F.2d 521, 526 n. 6 (Fed.Cir.1987). Furthermore, Barr points out that if an "applicant knows of information the materiality of which may so readily be determined, he or she cannot intentionally avoid learning of its materiality, even through gross negligence" lest he or she risk establishing the requisite intent to deceive. *Brasseler v. Stryker Sales Corp.*, 267 F.3d 1370, 1380 (Fed.Cir.2001).

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[39] Indeed, Mr. Nixon even admitted that he would have prepared the Ellman declaration differently (8T 118, 23-119, 1). Although Barr attempts to use this statement against Bayer to prove intent to deceive, the Court finds that this statement by Mr. Nixon bolsters his credibility because he recognizes that the declaration was imperfect.

Dr. Ellman, however, cannot be said to meet these standards. There is no evidence that Dr. Ellman was intentionally ignoring red flags that would have indicated the existence of prior art (or here, prior public use). Indeed, Dr. Ellman testified that he believed that the purpose of his signing of the declaration was to resist any allegation that the U.S. trials may be considered prior public use. Dr. Ellman's *carelessness* with regard to the declaration also belies the contention that he *intentionally* omitted or ignored evidence of alleged prior public use in the European trials. Coupled with his testimony that he did not even consider the European trials in concluding that the U.S. trials were confidential and experimental, Barr is hard-pressed to prove by clear and convincing evidence that Dr. Ellman intentionally deceived the PTO.

Barr also argues that Dr. Ellman breached his duty of candor with the PTO by stating that "[t]he activities concerning the Clinical Study were confidential, closely monitored by Bayer and conducted for the experimental purpose of determine [sic] the efficacy and safety of the Clinical Study Drug." (JX 10 ¶ 17). Barr contends that this statement is misleading because the study subjects in the U.S. trial were actually not closely monitored, were under no confidentiality obligation, and were given a large supply of the drug to self-administer with no restriction on use and dissemination. This information, Barr also contends, is critical to the issue of experimental use (and consequently, prior public use).

While the confidential nature of the U.S. trial is arguably material to a finding of whether the use was experimental (and therefore not a prior public use), this Court found above that the U.S. trials did

not lack confidentiality given the extensive confidentiality binding the principal investigators, and because the micronized nature of the drug was not disclosed to anyone, including the patients. Therefore, because the Court finds that the U.S. trial was, indeed, confidential and closely monitored, Dr. Ellman's statements to that effect were not false or misleading. Barr thus fails the intent element of the inequitable conduct test on this argument as well.

2. *Dr. Lipp*

Bayer's patent was rejected on September 13, 2001, on the ground that prior art taught that micronization could lead to increased bioavailability. In response thereto, Bayer submitted a declaration by Dr. Ralph Lipp, one of the inventors of the '531 Patent. The declaration cited to a number of articles which Dr. Lipp allegedly supported the proposition that the prior art indicated that "micronization of other drugs does not necessarily lead to increased bioavailability over other forms or can be detrimental to bioavailability." (JX 11 at ¶ 10). Barr argues that Dr. Lipp grossly mischaracterized the articles and that his statement is unsupported by the prior art and was intended to trick the patent examiner into issuing the approval on false pretenses. Barr's expert, Dr. Chambliss, opined that Dr. Lipp mischaracterized the cited articles (2T 99, 22-25); but Bayer's expert, Mr. Nixon, noted that as a whole, the articles supported Dr. Lipp's assertion (8T 113, 20 through 114, 17).

It appears that the examiner allowed the claims on July 2, 2004 in part based on Dr. Lipp's declaration, because the examiner found that "micronized drospirenone would degrade even more rapidly, as micronization exposed the drug particles to the acidic

environment of the stomach; and an oral dosage form containing the drospirenone particles, which exposed to the gastric environment upon dissolution, would be unobvious [sic] in view of the data presented in the declaration filed December 9, 2003." (JX 2 at p. 1722).

Barr contends that Dr. Lipp's statements in his declaration were material, and that he had the requisite intent to deceive the PTO to cause the examiner to withdraw his objection to the '531 Patent. With regard to materiality, it appears that the examiner actually relied—at least in part—on Dr. Lipp's declaration. Barr has more than satisfied its burden to prove that "a 'substantial likelihood [exists] that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent,'" *Fox Indus., Inc.*, 922 F.2d at 803 (citations omitted), since the record shows that the examiner actually relied on the Lipp declaration.[40]

However, Barr cannot satisfy its burden of clear and convincing evidence that Dr. Lipp had the intent to deceive the PTO by making inaccurate statements in his declaration. Barr does demonstrate that Dr. Lipp was inattentive to detail and maybe even

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[40] The examiner did not rely solely on the Lipp declaration, however. On July 2, 2004, the examiner also cited the Funke declaration filed on May 19, 2004, declarations filed on December 9, 2003 (JX 2 at p. 1722), and Bayer's reply to the patent rejection. As noted above, it is unclear what the examiner meant by "December 9, 2003" declarations. However, the examiner did find that the micronized drospirenone would degrade faster because micronization exposed the drug particles to the acidic gastric environment (JX 11, Lipp Decl. Appendix A at 0623), which suggests reliance on the Lipp declaration. The parties' experts don't appear to dispute whether the examiner actually relied on the Lipp declaration.

sloppy. Dr. Lipp failed to read at least one, if not more, of the articles cited in his declaration—or if he did read them, he at least had not read them in full or had not read them in any detail (Lipp Dep. 141:5-10, 133:3-14, 162:12-18, 166:3-4, 20-22, 168:18-23, 169:21 through 170:1). Furthermore, one abstract Dr. Lipp cited supports Barr's conclusions regarding micronization (Lipp Dep. 133:3-18). However, carelessness or sloppiness does not necessarily amount to intentional deception.[41]

First, Barr focuses on the term "other forms" in the declaration to prove intent to deceive. At Dr. Lipp's deposition, he was asked about the phrase "other forms":

> Q: What do you mean when you say, "does not necessarily lead to increased bioavailability over other forms"? What do you mean by "other forms"?
>
> A: That's a broad term including, for instance, non micronized form.
>
> * * *
>
> Q: When compared to what? You state that micronization does not increase to—lead to increased bioavailability, but compared to the bioavailability of what?
>
> A: Of other forms.

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[41] Barr also claims Dr. Lipp acted inappropriately because the prior art to which Lipp referred and submitted to the patent examiner were abstracts of articles obtained from a library service. Because the Court finds that Dr. Lipp otherwise lacked the intent to deceive the patent office, this argument does not win the day for Barr.

> Q: So not necessarily unmicronizing. It can be any other form?
>
> A: As I mentioned before, the term "other forms" is rather broad. It can include maybe unmicronized forms obviously but also other formulations.

(Lipp Dep. 160:18-22, 163:23 through 164:7).

While "other forms" may lack the linguistic clarity and preciseness that one would expect of a scientist, it is difficult to characterize the phrase as one crafted with the intent to be purposely deceitful.

To interpret "other forms" to refer only to the unmicronized form of drospirenone is to [sic] narrow a construction upon which to show intent to deceive. Dr. Lipp's explanation is plausible—he was referring to multiple alternate forms of the drug.

In looking at the articles Dr. Lipp cites, it is clear that his declaration was meant to not only compare different forms (i.e., micronized versus unmicronized) of the drug, but also to compare different *formulations* (i.e., solid dispersions, freeze-dried formulations) and different drugs altogether (i.e., triamterene). Given the variety of scenarios cited to in his declaration, it would be an unrealistically narrow reading of the term "forms" to conclude that Dr. Lipp was merely referring to the unmicronized version of drospirenone. This would mean all of the articles attached to the declaration would be completely off-point and misleading. Barr is hard-pressed to argue that Dr. Lipp's statements were intentionally misleading merely by narrowly construing what Dr. Lipp, himself, referred to as a "broad term *including, for instance*, non micronized form." (Lipp Dep. 160, 18-22).

Next, Barr contends that Dr. Lipp intentionally mischaracterized the articles cited in support of his declaration. Without a lengthy summary of all the articles, it is fair to say that the articles are not squarely on point. However, most are arguably relevant. The articles and/or abstracts include: (a) the *Montel* reference, which concerns agglomeration (Def. 2 at p. 4), a phenomenon results from micronized particles sticking together (JX 31, Montel 1983 at M-P00000968); (b) the *Arias* reference which concerns the bioavailability of two formulations of triamterene, one of which is micronized (JX 18); the *Berlin* reference, which compares a micronized formulation of a drug to a different formulation (a solid dispersion) (2T 109, 18-25); and the *Duclos* and *Fell* articles, which compare different formulations of a particular drug (JX 15; 2T 110, 8 through 111, 4).

In his video deposition, Dr. Lipp appeared to firmly believe that the articles he cited bolstered his ultimate point to the examiner that micronization does not always lead to increased bioavailability as compared to other formulations.[42] Furthermore, Dr. Chambliss conceded that Dr. Lipp's statement "micronization of other drugs does not necessarily lead to increased bioavailability over other forms or can be detrimental to bioavailability" is true standing on its own in other contexts (2T 106, 22 through 107, 3). Dr. Chambliss offered no opinion on Dr. Lipp's intent (2T 115, 9-11). Mr. Mossinghoff also offered no opinion on "whether anyone at Bayer Schering had an intent to deceive the Patent Office." (4T 119, 17-

[42] Although Dr. Lipp had not read some of the articles or had not read them in full (or recently), he discussed them at his deposition and thoughtfully explained why they support the proposition in his declaration.

20). Barr merely contends, without any proof, that because Dr. Lipp is an inventor of the '531 Patent and receives royalties therefrom, he has a motive to mislead the examiner in order to get the patent reissued. Similarly, Barr alleges that Bayer has a "strong motivation to mischaracterize the prior art" because Bayer seeks to extend the life of its monopoly for drospirenone for another twenty years.[43] While these two facts could be suggestive of motive to misrepresent, they can equally be construed as motives for Dr. Lipp to self-advocate by interpreting prior art in Bayer's favor—as one does in a patent application. Distinguishing prior art "does not constitute a material omission or misrepresentation." *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1482 (Fed.Cir.1986).[44] While the interpretations in

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[43] This argument, as applied to Bayer, is moot. As noted above, the duty of candor applies to individuals, and not corporations. Thus, the Court must focus its analysis on Dr. Lipp, and not Bayer as a whole. Barr also argued Bayer had similar motives for allegedly hiding the results of the European clinical trials with regard to the Ellman declaration. This argument is also moot on identical grounds.

[44] As noted above, the examiner seems to have relied on the Lipp declaration at least in part. When an examiner has the references to refer to during a patent examination, he is free to reach his own conclusion in the face of "attorney argument, attempting to distinguish the claims from the prior art." *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1349 (Fed.Cir.2007). An applicant's arguments supporting its patent application do not constitute inequitable conduct when the examiner has the prior art before him throughout the prosecution and, despite the applicant's attempt to distinguish that prior art, "[t]he examiner was free to reach his own conclusion regarding [the prior art]." *Akzo N.V.*, 808 F.2d at 1482.

The examiner here clearly came to his own conclusion about the prior art after reviewing Bayer's submissions, and reversed his prior rejections of the patent. Indeed, Dr. Mossinghoff testi-

the Lipp declaration may be unclear and not totally on point, the Court finds that Barr has not marshaled enough proof of intent to meet the clear and convincing evidence standard.

The Court finds that Drs. Ellman and Lipp did not engage in inequitable conduct with regard to either of their respective declarations.

IX.

CONCLUSION

Based on the foregoing facts and law, the Court finds that the disputed claims of the '531 Patent are obvious. Barr's contentions that there was a prior public use of the '531 Patent and that Bayer engaged in inequitable conduct in the prosecution of the '531 Patent are dismissed for failure to prove same by clear and convincing evidence.

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fied that he believed the examiner reviewed the documents on June 11, 2004, according to the Form 1449 (4T 116, 3-13). Mr. Nixon similarly testified that the signed Form 1449 would demonstrate that the examiner confirmed what items he reviewed during the whole prosecution (8T 112, 4-12; JX2 at p. 01725-26).

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

[Filed Oct 26 2009]

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellants, and a response thereto having been invited by the court and filed by the Appellee, and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on November 2, 2009.

FOR THE COURT,

/s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 10/26/2009

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* Amici Curiae, Eli Lilly and Company and the Pharmaceutical Research and Manufacturers of America, were granted leave to file a brief in support of the appellants' combined petition for panel rehearing and rehearing en banc. The American Intellectual Property Law Association was granted leave to file a brief as amicus curiae.